THE BRITISH JOURNAL

OF

OPHTHALMOLOGY

NOVEMBER, 1947

COMMUNICATIONS

A CONSIDERATION OF ANIRIDIA, WITH A PEDIGREE

BY

P. H. BEATTIE

NORWICH

Introduction

Two or three patients in the family which is the subject of this enquiry had been treated in Addenbrooke's Hospital, Cambridge. On enquiry it was found that the defect was common in various related sibships, and although the affected people were living in villages scattered through the fen country between Cambridge and Peterborough, it was thought worth while to visit them all and record the condition of their eyes. In the future, members of such a family as this are less likely to remain domiciled in one locality, and an observer's task will be more difficult by virtue of the distances he will be obliged to cover to collect data from them all. The congenital abnormality shown in this particular family is a rare one. Few pedigrees of aniridia have been published in

recent years. Many which are widely quoted in authoritative text-books are unreliable and have been constructed from second-hand reports. Many of the pedigrees collected by Julia Bell[1] are small and with little exact relevant detail. Julia Bell[2] has appealed for the suppression of the most remarkable aniridia pedigree published, that of Risley[3], in which aniridia is reported in 111 out of 119 relatives but it was confirmed in the case of one individual only.

Strictly speaking the term "aniridia" is not accurate as some vestiges of iris have invariably been found in eyes which have been sectioned[4], even though in life no trace was visible on ordinary clinical examination. The more limited term "irideremia" has been occasionally used but has not found general acceptance amongst ophthalmologists. For general purposes aniridia may be defined as "the entire absence of the iris or of a portion too great to justify the term coloboma."[5] Any fragment which does exist is functionally useless.

All living affected persons in this family have been visited in their homes and examined there. In some cases they have been brought to hospital for more precise examination with slit-lamp, etc. Refractive errors were determined in their homes with an electric ophthalmoscope. Intra-ocular pressure was estimated digitally. Almost all non-affected descendants of II 1 were examined and a search made for any slight or intermediate change in the iris.

Thirty-one patients were found with bilateral abnormality of the iris. The abnormalities varied in gravity and have been subdivided thus—

Four cases with coloboma of iris and/or hypoplasia of iris.

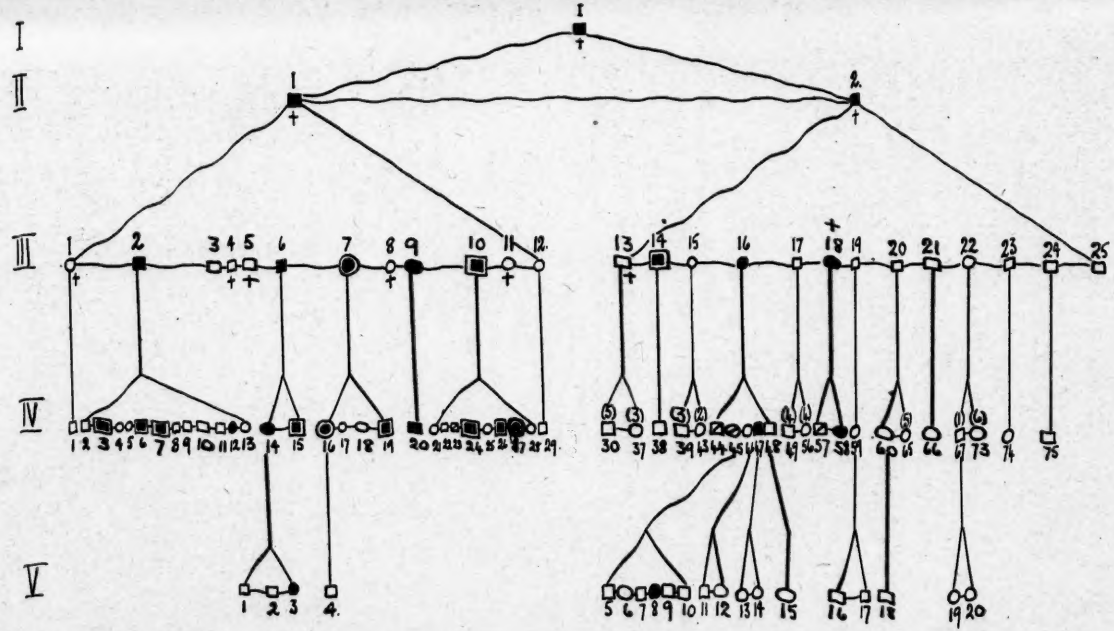
Ten cases with aniridia either partial or complete of both eyes.

Twelve cases with bilateral aniridia and ectopia lentis.

One case with partial aniridia in R. eye and coloboma in L.

Four cases were not examined. Generations I and II are dead, as is Case III, 18. Careful questioning of their children and relatives make it certain that these people suffered from aniridia, but one cannot say whether or not the lenses were dislocated. Aniridia itself is such an obvious abnormality that lay testimony can probably be accepted, especially where the person involved was one of the family circle.

It is apparent from inspection of the pedigree that the three varieties of abnormality follow no special pattern of distribution. Cases with ectopia of lens are sometimes children of parents with uncomplicated aniridia, and vice versa. Those with colobomata of iris (or hypoplasia of stroma) occur in sibships affected with



PEDIGREE OF FAMILY WITH CONGENITAL ANIRIDIA.

KEY.
- □ - NORMAL MALE
- ○ - NORMAL FEMALE
- ▨ - COLOBOMA AND/OR HYPOPLASIA OF IRIS (MALE)
- ⊘ - " " " " " (FEMALE)
- ■ - ANIRIDIA (MALE)
- ● - " (FEMALE)
- ▣ - ANIRIDIA WITH ECTOPIA LENTIS (MALE)
- ◉ - " " " " (FEMALE)
- (5) □ - NUMBER OF NORMAL CHILDREN
- † - PATIENT DEAD.

aniridia alone or with the graver condition of aniridia and ectopia lentis. A parent with coloboma is capable of transmitting the defect in a severer form to her children—IV 45 and V 8. The defects appear to occur in an unpredictable way amongst affected members. Unfortunately three of the colobomatous group have no children so that their genetic potentialities are not known.

Genetics

The defect is generally inherited from affected members of a family in a proportion of approximately 50 per cent. In this family 42 per cent. of the total descendants of II 1 are affected. Only 23 per cent. of the children of II 2 are affected, but the children of this 23 per cent. show an incidence of 62 per cent. Only affected members transmit the disease and normal children invariably have normal offspring. It therefore fulfils the conditions of a regular Mendelian dominant. In this family an affected person has invariably married a normal person and from this and the proportion of cases with aniridia we must assume the affected person is heterozygous—the mate in every case being homozygous for the recessive allelomorph. This may be illustrated by the following diagram[6]:—

One parent heterozygous affected

	Gametes	A	a	
One parent normal	a	Aa	aa	*i.e.* 50% heterozygous affected 50% normal
	a	Aa	aa	

Being a dominant character the trait becomes apparent in a heterozygote. There are no cases in this pedigree, or indeed in the relevant literature, of two heterozygotes for the condition marrying each other and it is therefore impossible to say what appearance a homozygote for the condition would present. It is possible that lethal genes would accompany the homozygote condition, as in the case of the yellow mouse quoted by Corner[7] and in numerous experiments with the Drosophyla. There is no accompanying infertility in aniridia as there is for example in neurofibromatosis[8], nor in this pedigree is there evidence of mental or skeletal defects. We must assume that in some ancestor of I the

condition arose as a gene-mutation and thereafter, as in other alterations of the germ plasm, the defect was transmitted in accordance with mendelian principles as a regular dominant. Nothing is known of the cause of gene-mutations in human beings, or indeed of mammals generally, but in the insect world the normal production of mutations can be multiplied by means of thermal, X-ray stimulations of the germ plasm[9]. Plenty of records exist of aniridia arising without any known hereditary predisposition[10, 11, 12] and in the case of a dominant of this type a new mutation must be postulated, especially where it is known that the defect is transmitted to approximately 50 per cent. of children[13].

In recent years an attempt has been made to assess the mutation rate for various human abnormal conditions. J. B. S. Haldane[14] began this work with a calculation of the mutation rate for haemophilia. Recently Mollenbach[15] has estimated the mutation rate for aniridia, on the basis of his findings in Copenhagen, to be between 1 :50,000 and 1 :100,000.

The presence of three types of defect in one family without any apparent order in their incidence presents a difficult genetic problem. It is known that in hereditary defects a good deal of variability exists in different families and indeed in different sibships of the same family[16]. It may be that the iris form and structure are governed not by one but by many genes and that in the defects of varying gravity different numbers of genes are responsible. Waardenburg[17] says "Since in the fruit fly Drosophyla—cytologically the most exhaustively studied animal—genes transmitting the colour of the eye or the appearance of the bristles have been found in every chromosome, it seems probable that the genes which determine normal structure and function of ocular tissues, and therefore those genes which determine their hereditary abnormalities, are distributed over several chromosomes." Environment can have no influence in a disorder where different primary defects occur in the same sibships and even between twins—IV 6 and 7. No consanguineous marriages are recorded in this pedigree. We must assume that "since there are families in which some have aniridia and others coloboma, whereas there are other families in which cases of coloboma occur in the absence of cases of aniridia, there must be distinct hereditary factors at work in the respective families, factors whose effects are quantitatively different."[18] With a view to determining whether the abnormal gene (or genes) is linked with normal hereditary factors, blood and "taste-testing" examinations of several separate sibships were performed.

[A]

Case	III 2	—	A_2
	IV 3		OIV
	IV 7		OIV
	IV 9		OIV
	IV 10		OIV

[B]

III 6	—	A_2	pp.	M	rr
Wife		O	P	MN	R_2r
IV 14	—	A_2	pp.	M	rr
IV 15	—	A_2	P	M	R_2r

[C]

III 7	— A_2	pp.	M	R_1R_2
Husband	O	P	MN	R_1r
IV 16	O	P	M	R_1R_2
IV 17	(Not taken)			
IV 18	A_2	P	MN	R_1R_2
IV 19	O	P	M	R_2r

[D]

III 10	A_2	pp.	M	R_2r
Wife	B	P	MN	R_1r
IV 21	B	P	MN	R_1R_2
IV 22	B	P	M	rr
IV 23	A_2B	P	M	R_2r
IV 24	A_2B	P	MN	R_2r
IV 25	B	pp.	MN	rr
IV 27	B	pp.	M	R_1R_2

[E]

III 16	P	MN	R_1r
Husband	P	M	R_1R_1
IV 44	P	MN	R_1R_1
IV 45	P	MN	R_1R_1
IV 46	P	MN	R_1r
IV 47	P	M	R_1r
IV 48	P	MN	R_1R_1

Note : Affected cases are underlined.

Taste-Testing with PHENYL-THIO-UREA.

A. *III	6	—	Taster
Wife		—	Non-Taster
*IV	14	—	Taster
*IV	15	—	Non-Taster

B. *III	7	—	Taster
Husband		—	Non-Taster
*IV	16	—	Taster
IV	17	—	Taster
IV	18	—	Taster
*IV	19	—	Taster

* Affected cases.

Taste-testing with PHENYL-THIO-UREA—*continued*

C. *III 10 — Taster
Wife — Taster
All children — Tasters

D.*III 16 — Non-Taster
Husband — Taster
*IV 44 — Taster
*IV 45 — Taster
IV 46 — Non-Taster
*IV 47 — Non-Taster
IV 48 — Not tested

* Affected cases.

These findings were scrutinized by Prof. R. A. Fisher, who thought there was slight statistical evidence of linkage to the ABO group. He considered greater numbers should be investigated and that the matter was worth pursuing. It was realized that even if linkage did exist the knowledge would be of no immediate practical value in a disability such as this which is present from birth (unlike Huntingdon's chorea where linkage with a known normal factor such as blood groups might enable a prediction to be made of those likely to develop the disease in later life[19]). Nevertheless it would be of some theoretical value as a contribution to the body of known linkages which must be enormously extended before substantial beginnings of a so-called chromosome map could be assembled for humans. At present a relatively complete map is a remote possibility, man being such a slow breeder and not available for controlled genetic experiments like the fruit fly Drosophyla from the intensive study of which so many facts have been learnt.

Embryology

No foetal eye affected with aniridia became available for study. It is obvious the disability is germinal : environment is not a factor of any importance, nor is it the result of any transplacental infection such as the foetal maldevelopments associated with maternal German measles[20]. Many theories have been advanced to explain the mechanism of its production and no general agreement has been reached amongst investigators. Foetal eyes affected with aniridia are rarely examined.

The presence of an anterior polar cataract suggested to Treacher Collins[21] that the defect was due to an abnormal and prolonged adhesion of the lens to the cornea (an analogous opacity is seen

after a perforated corneal ulcer). This would make it impossible for the iris to insinuate itself between these two structures. An anterior capsular cataract does occur in this pedigree, *e.g.*, III 9, but it is not generally present—in fact in the youngest members the lenses and capsules are quite clear. One would also expect such an adhesion to be accompanied by an opacity in the substantia propria of the cornea, but such an opacity is not found in this series.

The mesodermal theory in Ida Mann's words [22] suggests " the growth of the mesodermal iris is primarily abnormal and inhibits the normal forward growth of the ectoderm." Evidence has been adduced that colobomata of the iris are caused by the " abnormally long persistence of one, several or all the vessels which normally connect the circulus arteriosus iridis major with the terminal branches of the hyaloid vessel around the edge of the optic cup."[23] If all the vessels persist the growth of the iris would be impeded all the way round and the condition of aniridia result. The mesodermal iris which normally appears first would not perform the function of a scaffold along which the ectodermal elements could grow. Some support is lent to the mesodermal theory of genesis by cases IV 45, IV 44, IV 23; these have defects in the iris stroma only, with intact pigment layers beneath, suggesting at least that the defect is not due to ectodermal maldevelopment. These cases also have a marked proliferation of the pigmentary layers at the defective parts of the pupillary region, as though vigorous ectodermal tissue had attempted to close the mesodermal defect.

The ectodermal theory postulates that the rim of the optic cup which subsequently forms the neural layers of the iris does not grow forward at the proper time, that is at the 70-80 mm. stage[24]. This theory would be more in line with the " organizer " hypothesis, whereby the optic cup is believed to have a " governing " function calling forth the lens[25]. Evidence in its support is found in the ectodermal defects which accompany aniridia—absent fovea centralis, nystagmus, and anomalies of lens and retina. Nystagmus was found in 3 cases, choroido-retinal degeneration in 3 and (except for one case of nystagmus) all belonged to a sibship in which hereditary myopia was present—IV 2-13. In one case of nystagmus (III 9) a brisk foveal reflex could be seen on the R. side only, IV 13, a normal case in the same sibship had extensive peripheral pigmentation of the fundus in both eyes. The frequent incidence of ectopia lentis in this series may lend support to the ectodermal hypothesis, as this condition is thought to be due to a primary defect of the zonule, which results in a displacement of the lens when the ciliary ring opens out—the zonule being developed from tertiary vitreous and therefore an ectodermal structure[26].

Pathology

No first-hand facts can be given of the histology of the condition, as no eye in this family has become available for pathological examination. III 14 had the L. eye enucleated seven years ago, but no histological examination was made. The eye had been blind for many years and very red and painful for 5 months. Reports are not numerous in the literature, but all agree that a few tags at least of iris are found in every case of (clinically) complete aniridia[27]. Treacher Collins[28] says "Microscopical examination of these cases seems to show that they are really predisposed to glaucoma, for not only do we find that the ciliary body terminates in a rudimentary iris, which if pushed forwards is quite sufficient to block the whole of the posterior surface of the ligamentum pectinatum, but that between this rudimentary iris and the lig. pect. there are abnormal adhesions."

Corneal opacities are stated to occur, but they were not seen in this series. Lenticular opacities were common but of no single type and supported no particular embryological theory. Opacities become more widespread and severe as affected patients grow older and ultimately cause incapacitating visual defects. It may be noted that generalized opacity of the lens occurs most early in two cases where they were dislocated, IV 3 and IV 6. Presumably the liability to cataract formation is due to impaired nutrition of the lens. The iris normally has some share in the interchange of fluids in the eye and its absence may be assumed to have a deleterious effect. If the ciliary processes are small or absent as they are sometimes said to be[29] this would further interfere with the fluid interchange. Possibly the absence of the constant contraction and dilatation of the iris may remove a normal stimulus and be responsible for a more sluggish circulation in the ciliary body, which would prevent a vigorous interchange of intra-ocular fluid.

The development of a generalized opacity may be accompanied by a swelling of the lens, with pressure on the iridial angle and the onset of secondary glaucoma—III 16. Why the presence of an ectopic lens greatly increases the tendency to glaucoma is not altogether clear. This complication does not appear to be especially common in families with congenital ectopia lentis without aniridia. It may be that the elongated fibres of the suspensory ligament permit very minute movements of the lens to take place, movements which are not always clinically visible, and these may set up a chronic irritation leading to glaucoma.

Some writers have found histological evidence of an absent fovea centralis[30], which is assumed to be the cause of the partial amblyopia and nystagmus frequently encountered in aniridia.

Clinical findings

A. Cases with coloboma and/or hypoplasia of iris.

Mingled without apparent order amongst affected sibships are four cases exhibiting small colobomata and/or hypoplasia of the iris. These patients suffer no disability. Visual acuity is normal, with no tendency to formation of lens opacities nor of raised intra-ocular pressure. They occur in sibships with normal and aniridic brothers and sisters and in each case are themselves children of one affected parent. From one case it is evident that they may transmit the disease in a more severe form to their children, *i.e.*, IV 45 who is the least abnormal of all affected members of her sibship, having slight hypoplasia of the superficial layers of the iris stroma revealing in patches the deeper pigmented layers, has transmitted the malady in a more severe form to one of her six children—V 8. The other five children are normal. IV 23 has a R. pupil of normal size, but the superficial layer of the iris has gaps shaped like the petals of a flower, exposing the deeper pigmented layers. The L. eye has a dilated and very feebly reacting pupil with a coloboma of the superficial stroma of the iris at 5 o'clock in the pupillary margin, but the gap is filled in with a proliferation of the deeper pigmented layers. IV 45 has a coloboma of the pupillary margin of the iris at 9 o'clock in R. eye, with numerous areas of hypoplasia of iris stroma. The L. eye has a pupillary margin coloboma at 5 o'clock, the gap being partially filled with deeper pigmented layers. There are also areas of hypoplasia in the lower and temporal regions of the iris, with a small complete breach in the iris at 5.30 o'clock, forming a second very small pupil. He sees 6/5 comfortably with each eye and reads J.1. IV 57 has a small pupillary coloboma of the iris in each eye downwards and outwards, with areas of superficial hypoplasia just above and below the colobomata. His vision is excellent; he was accepted as A1 for the army and passed his eye test for the railway.

This tendency for colobomata and hypoplasia of the iris to occur in aniridic families is frequently noted in the literature. Licsko[31] noted atrophic anterior layers of iris in the child of an aniridic woman. Theobald[32] records a woman with an atypical coloboma iridis in each eye having a child with aniridia and congenital squint. De Beck[33], Cross[34], Foster[5], Polte[35] and others have recorded cases of intermingled aniridia and colobomata. In general it may be said that colobomata tend to occur in predominantly aniridic families, but Snell's family[36] exhibit the reverse finding—colobomata occurring in 5 generations with two individuals with aniridia. Complications are less frequent in

colobomatous eyes, but they do occur: *e.g.*, de Beck[33] records development of bilateral cataracts in a man aged 30 years, so disabling as to require extraction.

V 8 has a partial aniridia in the R. eye and a large coloboma of the iris of the L. eye directed downwards and slightly inwards. Such a case has been described by Waardenburg[37]. In this child the lower margin of the lens could be clearly seen in the red reflex, even though there is no displacement of the lens—presumably because in a child of this age the lens is relatively small, whereas later on when the lens grows larger, the edge is obscured by the sclerocorneal junction. (The lens margin can be seen all the way round in case V 3, aged 2 years.)

B. CASES WITH SIMPLE ANIDIRIA. (Ten cases.)

The two predominant symptoms are photophobia and poor vision. Photophobia is a source of greater discomfort in the younger patients. V 3 and V 8 are obviously very uncomfortable in ordinary light. IV 12 wears tinted glasses only in very bright light. IV 20 served in the Middle East for 3 years without any special discomfort. The ophthalmoscope light caused lacrymation to IV 16 but normally she was quite comfortable. The older members of this group appeared to suffer no discomfort except III 2 who habitually wore tinted glasses. He, however, had had a bilateral lens extraction. Hamilton[38] suggested that lack of photophobia was due to abnormal insensitivity of the retinal elements. It may be, as this family shows that the retina is sensitive at first and gradually becomes more accustomed to excessive light as the patient grows older. Significant also is the fact that the lenses of aniridic patients develop scattered opacities as the patients grow older.

In none of these cases does vision reach normal standards. The following table gives the salient features of these ten cases.

From this it appears that vision deteriorates as the patient grows older. Case V 3 had transparent lenses but was too young for determination of vision. Case IV 12, aged 14, had 1 dioptre of myopic astigmatism, but correction of this did not improve visual acuity. IV 20 had an error of +2·50 sph. each eye, but this correction did not improve vision. IV 12 had clear lenses, and IV 20 a small localized opacity in L. which probably did not interfere with vision, yet both had mediocre vision. As the ages progressed the lenticular opacities increased, with exception of IV 58, who had slight dusty opacities only in the centre of each anterior capsule. III 2 was aphakic, both lenses having been removed when he was 34 for mature cataract. III 16 had a completely opaque lens in her R. eye, and a slightly less opacity

Case	IRIS PRESENT	Lens opacities*	Tension	Vision	Refractive error	Vision with correction
V 3 (age 2)	NIL NIL	Clear	N	?	—	—
IV 12 (age 14)	NIL NIL	Clear	N	6/36 6/24	−1·00D. cyl. at 180°	Not improved
IV 20 (age 21)		—	N	6/24 6/18	+2·50 sph.	Not improved
IV 14 (age 28)	NIL NIL	—	N	6/24 6/18	?	—
IV 58 (age 30)		—	N	Not taken	+6·00 D. sphere	Vision good
IV 47 (age 32)		—	N	6/36 6/36	+6·00 D. sphere	6/12 6/12
III 9 (age 46)		—	N	6/18 6/60	+3·00 D. sphere	—
III 6 (age 50)	NIL	—	N	5/60 6/60	?	—
III 2 (age 57)	NIL NIL	Aphakic-lens extractions 22 years ago	N	H.M. Certified blind	Now +8·00D. sph. eye is essentially myopic	—
III 16 (age 62)		—	+ ±	Certified blind	?	—

(*) For details of lens opacities see case histories.

of L. III 7's vision has gradually declined: he was a soldier in the 1914-18 war. Thus it would appear that in the absence of lenticular changes vision is sub-normal from the beginning and that the opacities which accompany advancing years cause further gradual decline. Precisely why vision is poor in the absence of lenticular changes is not known. Some have produced histological evidence[39] that the macular area is abnormal, but no specimen from this series became available for pathological examination. A brisk foveal reflex was seen in a number of cases (see case histories). It has been pointed out by Alger[40] that the refraction of light both outside and inside the equator of the lens without the

iris diaphragm would cause a poor image and this lack of precision may deprive the macular area of effective stimulation in the early months of life when normal differentiation takes place.

Only in one case, III 16, was the presence of raised tension noted. The tension of the R. eye was higher than in L., but the rise was not marked. This is a small series, of course, and six of the cases are under 35 years of age. Nevertheless the findings are in striking contrast to those cases of aniridia complicated by ectopia lentis.

Although serious and incapacitating opacities of the lens in this small series have not developed until at any rate after the third decade, the literature records cases where a cataract showing "an expansion co-equal with the cornea" developed at 13[41], and another patient at 15 or 16 years had both opaque lenses broken up by a needle[42]. Foster[5] says that "Hirschberg watched a case from babyhood when the lens was clear and in place, until it was cataractous and shrunken and luxated at age of 10."

Glaucoma is generally accepted as a complication of aniridia. Foster[5], reviewing the European and American literature at the end of the last century, found it present in 12 out of 164 cases. Julia Bell[43], however, says "it would appear that there is no marked liability to glaucoma in the aniridic patient." Treacher Collins[44, 28, 45] repeatedly spoke of the greater predisposition of aniridic eyes to glaucoma, basing his opinion on histological evidence. Frost records a case in which one drop of homatropine precipitated an acute glaucoma (quoted in 38). In this family those with uncomplicated aniridia mostly have a hypermetropic error. From a survey of the literature this appears to be a common type of error[46, 44]. This fact may account for the convergent squint present in V 8, and frequently noted by other observers in aniridia. De Beck[33], examining a lens after extraction from an aniridic patient, noted that its nucleus was excessively broad and thin. Patients suffering from traumatic aniridia are said to suffer from no defect of accommodative power[41], but in this series it was noted that IV 58 with an error of +6·00 D. though only thirty years old, saw more satisfactorily with a second more powerful pair of glasses for close work, as did IV 47. IV 12 belongs to a sibship affected with myopia. This defect is not uncommon in aniridia families. Blair and Potter[47] have recorded two aniridic children of a colobomatous father, each child with high myopia and astigmatism. Foster[5] records it as a common accompaniment of aniridia.

C. CASES WITH ANIRIDIA AND ECTOPIA LENTIS. (12 cases.)

In this family twelve patients have the additional primary complication of ectopic lenses as well as aniridia. The principal

features are briefly summarized in Table E. As in aniridia alone, photophobia is troublesome early in life. It is, for example, marked in IV 27 and her two brothers, IV 26 and IV 24, but in older patients the symptom is not complained of. Whether this is due to an acquired insensitivity of the retinal elements or to the development of corneal opacities is not easily decided. In general visual acuity is poorer than in uncomplicated aniridia, especially in such cases as IV 15, IV 19, IV 24, where the lower edge of the lens traverses the central portion of the large pupil and further interferes with the refractive system of the eye.

In each case the patient preferred, where he had the choice, to look through the phakic part of the eye, except III 7 who was helped by a +11·00 D. sphere correction in R. eye, even though the lens was not dislocated upwards as far as the centre of the cornea. The first three cases have a mixed astigmatism, myopia and hypermetropia "with the rule." IV 24 and IV 26 were slightly helped by the appropriate correction. IV 3, IV 6, and IV 7 were not refracted but had gross signs of myopia in the fundus, with marked evidence of retino-choroidal degeneration. In this sibship myopia was inherited from an affected aniridic father, III 2. IV 16 had a moderate hypermetropia; correction did not improve her distant vision, but was a considerable help with near vision. III 10 had a hypermetropic astigmatism; correction improved his vision slightly.

Cases V 24, 26, 27 and III 10 were examined with the slit-lamp. Cases IV 24 and 26 and III 10 showed the elongated fibres of the suspensory ligament below, placed regularly with no gaps and with a sturdy vitreous behind. IV 27 showed irregular fibres with a gap in the vertical meridian and a grossly degenerate vitreous behind. In IV 15 the suspensory ligament could be clearly seen with a loupe. The mixed astigmatism noted in cases IV 24, 26 and 27 could be explained by the weaker pull of the suspensory ligament below compared with the fibres laterally. None of these cases showed a highly myopic retracted spherical lens correctable with a −14·00 D. sphere, indicating complete absence of traction by the suspensory ligament[48].

Only in the two youngest were the lenses quite clear. Opacities developed in the second decade, but there was no regular gradation of density as the patients grew older. Dense cataracts were present in IV 3 and 7, whereas III 10, who is much older, had milky opacities present in both nuclei and a suggestion of lamination in the rest of the lens. On making a fundus examination one was conscious of a slight distortion in some cases, probably due to tilting of the lens. In no case was a coloboma of the lens observed. Tremulous lenses were observed in cases IV 24 and IV 3. Rayner

Case	Displacement of lens	IRIS	Visual acuity	Tension	Refractive Error	Lens opacities*
IV 27 Age 7		None	R. L. H.M. 6/36	++ +	Mixed astigmatism	—
IV 26 Age 11		None	6/36 6/60 with glasses 6/36 6/36	++ ++	Mixed astigmatism	—
IV 24 Age 15		None	6/24 6/36	+ ++	Mixed astigmatism	—
IV 15 Age 15		None	6/24 6/36	Normal	Not refracted	—
IV 19 Age 18			6/60 6/24	++ N¹	Not refracted	—
IV 7 Age 19		None	Blind	Normal	Myopia	—
IV 6 Age 21		None	Blind	++ +	Myopia	—
IV 3 Age 28		None	Blind	++ ++	Myopia	—
IV 16 Age 32		None	6/36 6/60	Normal	Hyper-metropia	—
III 10 Age 44			6/60 6/24 with glasses 6/36 6/18+	Normal	Hyper-metropic astigmatism	—
III 7 Age 49		None	1/60 <6/60H.M. with glasses 6/60 <6/60H.M.	Normal	Not refracted	—
III 14 Age 64			Blind	++ L. eye enucleated for glaucoma	?	—

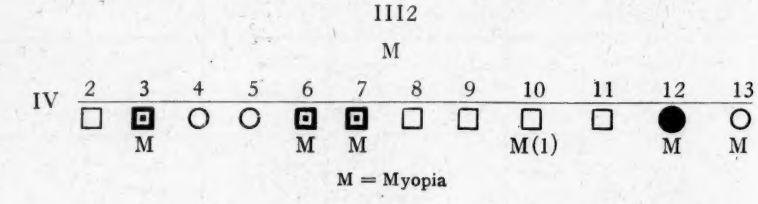
(*) For details see case histories

Batten[49] has recorded a case of bilateral aniridia and ectopia lentis: the R. lens was opaque and the L. partially so at 21 years old. The patient had never seen with the R. eye, but saw with the L. till she was 13 years old. Glaucoma had already developed.

The most striking difference on comparing these 12 patients with the ten having primary uncomplicated aniridia is in the incidence of glaucoma. Seven patients with ectopic lenses have glaucoma, whereas only one of the aniridia patients has slightly raised tension and she is the oldest of the group. Here IV 27, aged 7 has bilateral glaucoma, with an atrophic cupped disc observed, though in some eyes it was difficult to see the disc clearly or at all. Presumably the development of glaucoma is encouraged by the presence of ectopic lenses, but it is not clear why this should be so. Families showing ectopia lentis alone as a hereditary abnormality do not normally have a very high incidence of glaucoma. It will be observed that in five of the seven cases of glaucoma here there is no clinical evidence of any iris tissue present, and this, with possibly the particular formation of the iridial angle, may be a contributory cause of the raised tension.

Miscellaneous findings

The ocular defect is not accompanied by any skeletal abnormality, as, for instance, arachnodactyly, which is sometimes associated with congenital ectopia lentis. There are, however, some miscellaneous defects in the family which may be noted here. IV 7 is excessively fat, with a lazy good-humoured temperament suggestive of a pituitary dysfunction. X-ray examination of the skull revealed "a sella of physiologically small type." His twin brother, IV 8, is normal in all respects. Whilst hypermetropia is the predominating refractive error in this family, one sibship is found in which myopia is inherited from an affected father.



III 2, IV 3, IV 6 and IV 7 are all certified blind. IV 10 has myopia in R. eye only. IV 2 has a small myopia and astigmatic error (with aniridia). IV 13 has about 3 dioptres of myopia in

each eye. Stephenson[10] records myopia of 6·00 D. in two members of an aniridia family, but in general hypermetropia appears to be more common. Blue sclerotics are found in one sibship—IV 24, IV 26 and IV 27. In IV 24 the sclerotics are duck-egg colour, but a deeper shade of blue is present in cases IV 26 and IV 27. In all three cases the anomaly is associated with aniridia, ectopia lentis and secondary glaucoma. Blue sclerotics are recorded in an aniridic family by Mohr[50].

Mental defect associated with aniridia is reported by Velhagen[51], L. Polte[35], Stephenson[10]. No cases of subnormal intelligence were encountered in this family, either amongst normal or affected members. A particularly robust sense of humour is noteworthy in many members.

Nystagmus is reputed to be a common finding in cases of aniridia[52, 53]. Here it was met with three times only—in cases IV 3 and IV 7 and III 9. Cases IV 3 and IV 7 are both certified blind, as stated above in connection with myopia. Case III 9 has a vertical nystagmus, the oscillations being so fine that they are discerned only on ophthalmoscopic examination. In the R. eye, which has 6/18 vision, a brisk foveal reflex can be observed. Vertical nystagmus was observed by J. B. Lewis[46] in one case of an aniridic family.

IV 24 has corneae measuring 9 mm. in diameter transversely, with slight ptosis and defective dental enamel. H. Page[53] mentions micro-cornea and microphthalmos in an aniridic family, as does A. H. Benson[54], whilst Hamilton[38] and Stephenson[10] record defective dental enamel.

Two sibships were examined for colour vision and found to be normal. A curious inability correctly to pronounce the sibilant " S " was noted in the one sibship. The phrase " seen inside " becomes " shleen inshlide."

						II								
						2								
						L		L		L	L	L		
III	13	14	15	16	17	18	19	20	21	22	23	24	25	

L = Lisping

None of the children of affected members has this lisp, nor from enquiries made does it appear to have been present in the case of II 2 or his wife. The mouths were not examined for any abnormal attachments of the tongue.

Treatment

(*a*) Cases with colobomata and/or hypoplasia require no treatment.

(*b*) In cases with aniridia the photophobia, in this family at least, appears to be adequately relieved by dark glasses. McKie Reid[55] has recorded a case where an adult with aniridia was relieved of his discomfort in bright light by wearing contact lenses with an artificial iris and a central pupil of normal size. His vision was improved to 6/9 by this treatment and troublesome photophobia abolished. This method may be applicable to adults, but in this series it is the children who complain mostly of discomfort. Alger[40] suggests tattooing of the cornea as being effective in cutting out peripheral light rays thus abolishing photophobia and maintaining an effective stimulus of the macula, which may be necessary for its normal development. He records a marked improvement in a young girl whom he treated in this way. This method might be satisfactory in young children if a satisfactory technique of tattooing were employed.

For the glaucoma which develops in aniridia trephining may be tried, but there is little reason to suppose it is effective in reducing tension. Wiener and Alvis[56] bluntly say operative treatment is hopeless. In this series IV 12 had a prophylactic trephine at seven years of age (she is now aged 14 years), but no filtration bleb is visible. She has retained a normal tension, but so have other untreated cases. Hudson[57] records the case of a baby aged 7 weeks with aniridia and bilateral acute glaucoma, which was relieved by a paracentesis and subsequent trephine operations. Satisfactory intra-ocular pressure was established, but there is no record of the case being followed up. III 14, the only one in the uncomplicated aniridia cases with raised tension, has bilateral cataracts: it may be the development of cataract has been accompanied by some swelling of the lens which has helped to block the iridial angle with rudimentary iris tags.

Eyes with aniridia have an undoubted predisposition to early lens changes, as this series abundantly shows. If the opacities proceed to cause serious impairment of vision, ordinary extraction of the mature lens does not appear to be accompanied by serious technical difficulty or risk. III 2 had a mature lens removed from each eye without any complication and went back later for capsulotomy. There is no report in the literature of a series of extractions in aniridia. De Beck[33] gives an account of extraction of lenses in two brothers, one with aniridia and the other with bilateral colobomata. Vitreous was lost and cyclitis occurred in each eye, but ultimate vision was good in one eye in each patient

—in each case the eye in which cataract had developed more recently, which led De Beck to suppose that undue delay in operating on an aniridic cataract might make the prognosis poorer. Foster[5] wrote that " a number of operators have testified that a greater degree of cyclitis or other destructive inflammation attends their removal than is usually the case." This may possibly be due to the aniridia eye being relatively less vascular in the anterior segment, having no iris framework for vessels, and in consequence, less able to absorb foreign protein from the lens and overcome any slight infection. The risk of complications should not deter an operator from attempting to remove an opaque lens. The patient has nothing to lose. Possibly an intracapsular extraction would be less likely to be attended by subsequent inflammation as there would then be no irritating lens protein left in the anterior chamber. Treacher Collins[44] records an extraction where the patient regained vision 6/24 with +16 D., and J.4 with +20 D. In younger patients the cataract may be broken up by a needle and will sometimes rapidly absorb[42], but a rise of tension may occur necessitating repeated paracentesis[58].

(*c*) *Aniridia with ectopia lentis.*—As in uncomplicated aniridia, photophobia may be relieved by dark glasses. Tattooing the peripheral areas of the cornea would obscure the lens and make estimation of its later condition difficult. In this series an attempt was made to improve vision by correcting the refractive error. Where possible to make an accurate estimation, refraction through the lens was found to be a mixed astigmatism, due presumably to the unequal pull of the zonule fibres. Correction in a few instances, *e.g.*, III 10 and IV 24, made a little improvement. In no case was the lens found to be highly myopic, which would be expected if the suspensory ligament were defective in its whole circumference, a condition sometimes found in familial ectopia lentis and congenital microphakia. In one case only, III 7, was it possible to improve vision by an aphakic correction, and this in spite of the fact that the lens came well down in the pupil.

It is difficult to escape the conclusion that it is the ectopia lentis in combination with aniridia which is responsible for the high percentage of glaucoma in this series. To prevent the development of glaucoma by an early attack upon the lens would therefore appear to be the most rational procedure. Development of opacities in the lens are not necessary to produce glaucoma. The presence of an atrophic and cupped disc on R. side and raised tension on L. in case IV 27 at the age of seven years suggests that treatment at the earliest possible age is indicated. As removal of the lens would be a very hazardous procedure, almost certain to be accompanied

by vitreous loss on account of the difficulty of getting behind an upwardly dislocated lens, the first measure should be a needling of the lens in the hope of rapid absorption. If this were successful the eye would then be in the position of aniridia only with its more favourable prognosis, and the awkward optical disabilities caused by a dual refractive system would be removed. It would be possible to make a simple aphakic correction without the intervention of the lower border of the lens. If raised tension should develop after absorption of the lens, a trephine could be tried.

Case Histories of Aniridia Family

I 2. This man's eyes are known to have been abnormal.

II 1. According to his eldest son, this man's eyes were affected with the family complaint, but he was able to work as an agricultural labourer till well over 70. When very old he could see to fell trees and, in fact, was never obliged to retire because of poor sight.

II 2. J. W. This man's vision began to deteriorate when he was about 58 years old. He had looked after a pumping station in the Fen country satisfactorily, but during the last 20 years of his life his vision was very defective.

III 1. Deceased. Had normal eyes.

III 2. W. G. W., aged 57 years. This man's vision was never very good. It began to deteriorate seriously about 30 years ago. In 1922 he was admitted to the Royal Eye Hospital for a R. extraction and needling, and the L. eye was operated on in the following year. The lenses were opaque but there is no reference to ectopia lentis.

There is no clinical evidence of the iris. Both eyes are aphakic: some posterior capsule is visible in both eyes. Tension—normal both eyes. Refraction—+8·00 D. sph +2·00 D cyl. at 180 deg. Both fundi show myopic crescents and some central retinal degeneration. L. eye has a marked divergent squint. Vision—hand movements only. Prefers to wear slightly tinted glasses.

III 3. Normal eyes and vision.

III 4. III 5. Both males which died in infancy. Their eyes were normal.

III 6. Mr. S. W., aged 50 years. This man was in the 1914-1918 war. He now works in a brickyard and rides a bicycle to his work. Does not wear glasses. He gets very slight photophobia in bright light.

R. eye:—Complete clinical aniridia present. Tension normal. Slight central anterior lens opacity present and a wedge-shaped opacity which appears to involve whole thickness of lens at 5 o'clock. Vision—5/60.

L. eye:—Very narrow strip of iris present on nasal side. Tension normal. Milky nuclear opacity of lens present and a wedge-shaped opacity at 5 o'clock, as in other eye. Vision 6/60.

Patient himself thinks his vision has not declined in recent years, but his brothers are quite sure it has. No abnormality seen in fundi, but foveal reflexes could not be seen on account of lenticular opacities.

III 7. Mrs. F. M. This woman is a housewife. She has brought up four children and still manages to do house work.

R. eye:—Complete clinical aniridia present, with upward dislocation of lens. Slight opacities present throughout lens. Fundus seen through aphakic area appears normal. Tension—normal. Can read J.10. Distant vision is 1/60, but with a +11·00 D. sphere vision improves to 6/60.

L. eye:—Marked divergent squint present. Complete clinical aniridia, with upward dislocation of lens. Moderately dense opacities present throughout lens. Fundus not seen through aphakic area on account of vitreous haze. Vision—hand movements only. Tension—normal.

III 8. Female baby which died in infancy: normal vision.

III 9. Mrs. H. W., aged 46 years. This woman, unlike her brothers and sisters, has worn glasses for many years. A very fine *vertical* nystagmus is present in both eyes.

R. eye :—A narrow fringe of blue iris is present round the whole circumference. with a gap between 4 and 6 o'clock. The iris has a dark pigmented fringe, which looks like proliferation of the ectodermal layers. A small central anterior polar cataract is present with a circle of less dense opacities on the anterior capsule, paracentral in position. Vision 6/18: wears about +3·00 D. spheres. Macular area seen on this side, with brisk foveal reflex.

L. eye :—A narrow fringe of iris, blue in colour, is present, except for a gap between 3 and 5 o'clock. A central anterior polar cataract present, with a paracentral ring of capsular opacities. Fundus normal, except that foveal reflex could not be observed. Vision 6/60.

III 10. Mr. S. W., aged 44 years. This man is not troubled in bright light. Beyond 5 or 6 yards away he cannot recognize anybody. Is an agricultural labourer.

R. eye :—Very narrow fringe of iris present on nasal side. Lens is dislocated upwards and slightly outwards. With slit-lamp regularly disposed fibres of the suspensory ligament could be clearly seen in the aphakic part of the eye. The lens showed a central nuclear milky opacity, with opacities surrounding this showing a tendency to lamination. Slight tremulousness of lens seen with slit-lamp. Tension—normal. Vision R. 6/60, improved to 6/36 with + 1·50 D. cyl. at 170°.

L. eye :—Condition of iris and lens as described in R. eye. Lens slightly tremulous when viewed with slit-lamp. Tension—normal. Vision 6/24; with +0·75 D. sph. + 1·0 D. cyl. 90° vision improves to 6/18+.

III 11. Female child which died in infancy. Eyes normal.

III 12. Mrs. P. M., aged 40 years. Slight hypermetropic error (+1·00 D. sphere), otherwise eyes are normal.

III 13. Mr. W. W., deceased. Eyes were normal.

III 14. Mr. E. W., aged 64. This man's vision has always been poor, but 10 or 11 years ago it became too bad for working. Prior to that he could work in the stockyard if cattle were brought to him, but he could not work in the fields.

R. eye :—A very narrow fringe of iris is present in the upper nasal quadrant, extending from 12 o'clock to 4 o'clock. The lens is ectopic, displaced directly upwards. Lens is opaque throughout, but less so in the upper nasal and upper temporal periphery. Lens is tremulous. A good red reflex is visible in aphakic part of eye, but no view of retina could be obtained as vitreous is hazy. Suspensory ligament could not be seen below. Tension—+ +. Vision—perception of light.

L. eye :—This was enucleated seven years ago following five of pain and redness in the eye. It had been blind for many years. Unfortunately, a pathological examination of the eye was not made.

III 15. Mrs. M. A. G. Normal eyes and normal vision.

III 16. Mrs. E. T. Patient is a housewife who brought up five children. She saw fairly well until about seven years ago, when her vision began to fail. Earlier in life she was tried with glasses, but these did not help her.

R. eye :—Partial aniridia present. A narrow band of blue iris extends from 9 o'clock to 5.30 o'clock, with a deeply pigmented inner fringe. The lens is uniformly opaque, having a mother-o'-pearl appearance. There is good projection of light in the eye. Tension—slightly raised.

L. eye :—Divergent squint present. Has never been able to see much with this eye. Partial aniridia present: the iris is slightly broader than on R. side, being completely absent between 6 o'clock and 3 o'clock. Paracentral opacities are present posteriorly in the lower temporal and nasal quadrants of the lens. Slight hazy opacity is present throughout the lens. The fundus can be faintly seen through the lens and appears normal. The appearance is that of a hypermetropic eye. Tension—slightly raised.

III 17. Normal eyes.

III 18. Mrs. A. R., deceased. This woman had abnormal eyes, but whether she had ectopia lentis is not known. She died of carcinoma at age of 54, but

for some years before her death vision had deteriorated very much. She had a lisp.

III 19. Mr. F. W. Normal eyes.
III 20. Mr. A. W. Normal eyes. Has a lisp.
III 21. Mr. Z. W. Normal eyes.
III 22. Mrs. F. L. Normal eyes. Has a lisp.
III 23. Mr. L. L. Normal eyes. Has a lisp.
III 24. Mr. H. W. Normal eyes. Has a lisp.
III 25. Mr. S. W. Normal eyes.

IV 1. Has normal eyes.

IV 2. Mr. J. W. Has normal eyes and good vision. Was recently discharged from the Army and now works as a signalman on the railway.

IV 3. Mr. W. G. W. This man was certified as blind at age of nine years. Prior to that he had been able to see to go to school. He is now a basket-maker.

R. eye:—No iris visible. Lens is displaced upwards and outwards into the upper temporal quadrant of the cornea. It is uniformly opaque. A good view of the fundus is obtainable through aphakic area: the retina shows extensive central degeneration. Disc is very pale. Tension—++. Vision—no perception of light.

L. eye:—No iris visible. The lower part of the displaced lens is present in the upper nasal quadrant of the "pupil" and is uniformly opaque. It is also tremulous. The fundus cannot be seen through the aphakic area on account of a very hazy vitreous. Tension—++. No perception of light present.

IV 4. Miss M. P. W. Eyes normal. Vision 6/5:6/5.

IV 5. Miss V. W., aged 24 years. Eyes normal, apart from chronic blepharo-conjunctivitis.

IV 6. Mr. K. W. This man works in a blind institute as a basket-maker.

R. eye:—Complete clinical aniridia. Lens is displaced upwards. There is a very circumscribed dense opacity, central in position, involving the capsular and subcapsular tissues. Lateral nystagmus present. R. disc is pale and atrophic and the whole fundus has appearance of a very myopic eye. Tension—+. Vision—approximately 1/60.

L. eye:—Complete clinical aniridia. Lens is displaced upwards and slightly nasalwards. Slight superficial central opacities of the lens. Vitreous is hazy on this side, but fundus appearance suggests greater myopia than on R. side. Tension ++. Vision—1/60. Nystagmus present.

IV 7. Mr. R. W., aged 19 years. This boy is certified blind. He works at home, working in a small timber business. He is very fat, rather lazy, but generally very good tempered. X-ray of the skull shows a "sella of physiologically small type." He is just able to discern light and darkness.

R. eye:—No iris visible. The lens is displaced upward and slightly towards temporal side: it is opaque and of pearly colour. Inferior to the lens, through the aphakic part of the eye, a dense mass of connective tissue strands can be seen in the vitreous on the temporal side. The fundus cannot be seen. Tension—normal.

L. eye:—No iris visible. The lens is displaced upwards, its lower border reaching about half way down the vertical diameter of the cornea. Diffuse opacities prevent ophthalmoscopic examination through the lens. The retina can be seen through the aphakic area: gross retino-choroidal degeneration is present in the central area, and the eye is obviously a very myopic one. Tension—normal.

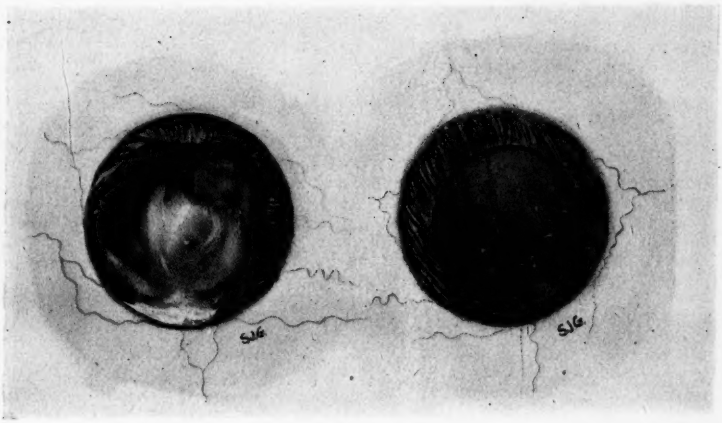
IV 8. C. W. This boy is a twin with IV 7, presumably a fraternal twin as there is little physical resemblance. Has a traumatic ptosis of L. eye, but otherwise his eyes are quite normal.

IV 9. P. W. This boy has just been discharged from the Marines. His eyes and vision are normal.

IV 10. F. W. No anatomical defect of eyes. L. eye is emmetropic, R. has 4 dioptres of myopia.

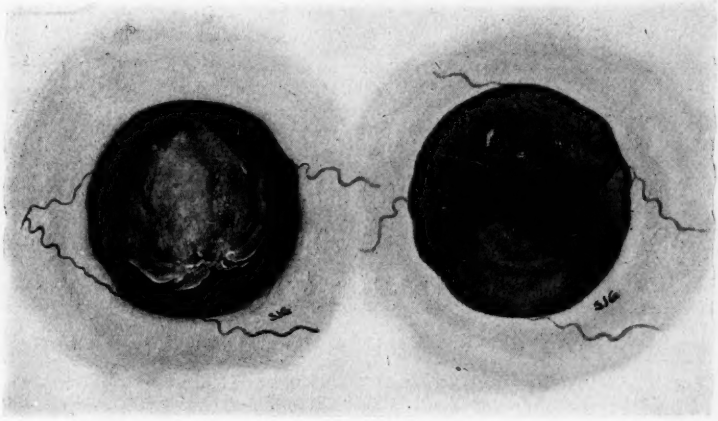
IV 11. C. W. Died at age of 5 months. Eyes were normal.

IV 12. G. W. This girl works as a hospital ward maid. Wears tinted glasses in very bright light. Bilateral trephine operation 7 years ago, but no filtration bleb can be seen.

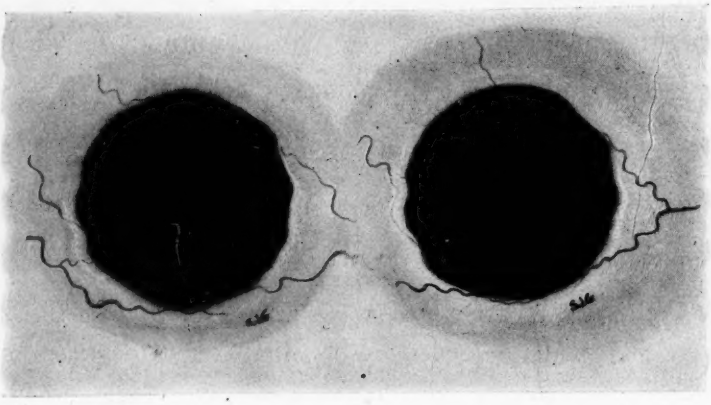


III 16, Mrs. E.T.

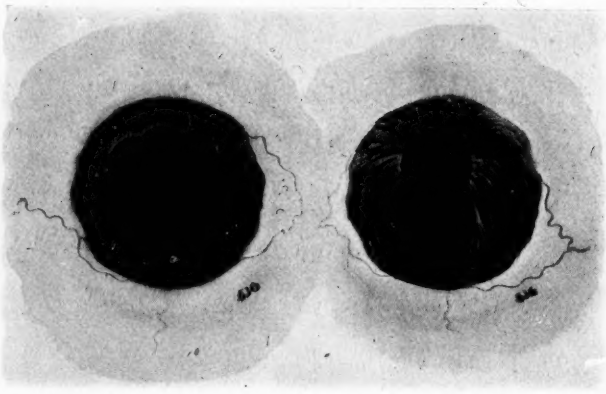
R. eye, focal illumination. L. eye, red reflex.



IV 7 (R.W.) R. eye, focal illumination. L. eye, red reflex.



IV 27. R. eye, red reflex. L. eye, red reflex.



V 8. M.S., aged 4 years, focal illumination.

R. eye :—No iris visible. Lens in normal position and quite clear. Tension—normal. Vision—R. 6/36: small myopic and astigmatic error present, but vision is not improved by this correction.

L. eye :—No iris visible. Lens in normal position and clear. Tension—normal. Vision—L. 6/24. No improvement with small myopic and astigmatic correction. Both fundi normal, but poorly pigmented. Near vision with both eyes together *is J.4.*

IV 13. S. W., aged 13 years. This girl has 3·0 dioptres of myopia. Both retinae show numerous small pigmented spots in the periphery. A large arterial loop is present on L. optic disc, extending forwards into the vitreous.

IV 14. D. W. Says she has slight discomfort in bright light. Examination with ophthalmoscope causes some lacrymation.

R. eye :—No iris visible. Lens is in normal position. Scattered opacities are present on anterior capsule and in anterior cortex of lens, especially peripherally. *Fundus normal; foveal reflex seen. Small hypermetropic error present.* Tension—normal. Vision 6/24.

L. eye :—No iris visible. Lens clear and in normal position. Fundus normal: macular area normal, with brisk foveal reflex. Tension—normal. Small hypermetropic error present. Vision 6/18.

IV 15. Aged 15 years. Works on the land. Does not wear glasses. Cycles to his work.

R. eye :—No iris visible. Lens displaced upwards and slightly towards temporal side. Small grey opacities present in periphery of lens. View of fundus through the lens is distorted (? due to some tilting of the lens). Through the aphakic part the fundus appears to be normal: a good foveal reflex present. With a loupe the elongated fibres of the suspensory ligament can be clearly seen below the lens. Tension—normal. Vision—6/24.

L. eye :—No iris visible. Lens displaced upwards, with fibres of suspensory ligament clearly visible with loupe. Slight diffuse opacities present in lens. Disc visible through both lens and aphakic part. Foveal reflex not seen on L. Vision—6/36. Tension—normal. With both eyes can read J.4, holding print very close to eyes.

IV 16. Mrs. E. S., aged 32 years. Says she sees well, but is "a bit short-sighted." Not troubled by photophobia. She sees exceptionally well at night. Both corneal are small

R. eye :—No iris visible. Lens displaced upwards very slightly. Very slight central anterior opacity of lens, with more marked paracentral opacity. Tension—normal. Vision—6/36. Reads J.12.

L. eye :—No iris, and lens dislocated as in R. eye. Slight paracentral opacity in lens anteriorly. Tension—normal. Reads J.14. Vision—6/60.

This woman has +3·00 dioptres hypermetropia in both eyes. Correction does not improve distant vision, but helps considerably for near work.

IV 17. I. M., aged 28 years. Normal eyes. Vision 6/6 : 6/6.

IV 18. I. M., aged 19 years. Normal eyes. Vision 6/6 : 6/6.

IV 19. Mr. O. M., aged 18 years. Works as farm labourer. Has very good physique.

R. eye :—Slight fringe of brown iris present above, extending from 9.30-3.30 o'clock, with a slight constriction at 1 o'clock. Lens is dislocated upward and slightly nasalwards, with lower edge of lens midway across the anterior chamber. Lens is slightly opaque throughout, with denser opaque dots in lower periphery. Vitreous slightly hazy. Fundus not clearly seen, but peripheral parts appear to be healthy. Tension—+ +. Vision—6/60.

L. eye :—Slightly wider fringe of iris present, extending from 7.30-3.0 o'clock. Lens dislocated upwards and nasalwards. A wedge-shaped opacity present in posterior part of lens between 4-5 o'clock but lens otherwise clear. Vitreous clear. *Tension—normal. Vision—6/24. Reads J.6.*

IV 20. Mr. W. W., aged 22 years. This man served in the army in the Middle East. He was not particularly troubled by photophobia.

R. eye :—An extremely narrow fringe of blue iris is present on nasal side between 2-5 o'clock. Lens in normal position. Fundus—normal. Tension—normal. Vision—6/24. Good foveal reflex seen.

L. eye :—Very narrow fringe of iris present except between 2.30-5.0 o'clock where there is complete absence. At 9 o'clock and at 12 o'clock there is a proliferation of pigmentary (posterior) layers of iris. There is a small dense localized opacity on anterior capsule in lower temporal quadrant of lens. Fundus—normal. No foveal reflex seen. Tension—normal. Vision—6/18.

Both eyes have a hypermetropic error of +2·50, but this correction does not improve vision.

IV 21. Miss N. W. Normal eyes.

IV 22. B. W. Normal eyes.

IV 23. D. W.

R. eye :—The green stroma of iris has five gaps in it, shaped like petals of a flower, revealing the pigmented deeper layers. Pupil is of normal size. Fundus—normal. Vision—6/6 and J.2.

L. eye :—There is a partial (pupillary) coloboma of iris at 4.30 o'clock. The gap in the superficial stroma is filled in with proliferated pigment layers, so that pupillary red reflex is quite circular. Pupil reacts very feebly to light. Fundus—normal. Vision—6/6 and J.4.

IV 24. S. W., aged 15 years. Marked photophobia in bright light. Sclerotics are " duck-egg " blue shade. Corneae are small (9 mm. horizontal diameter), some ptosis present and palpebral fissure small. (An attempt was made to take a Schiötz reading, but there was insufficient room to accommodate the base of the instrument between the opened lids. Dental enamel is defective.

R. eye :—Complete clinical aniridia present. Lens dislocated upwards. Elongated fibres of suspensory ligament clearly seen below with slit-lamp. Lens has diffuse slight opacities, but of no special distribution. Lens slightly tremulous and appears to be tilted backwards above. Tension +. Mixed astigmatism present, but will accept only -3·00 D. cyl. at 165 deg., with which he sees 6/24. This is the same as without glasses, but definition is better. Good view of fundus through lens and aphakic portion of eye. Fundus—normal.

L. eye :—Aniridia complete. Position and condition of lens as for R. eye. Tension + +. Mixed astigmatism present, but accepts -2·00 D. cyl. at 180°, with which he sees 6/36. Good view of fundus not obtained because of slight vitreous haze. Lens slightly tremulous. Elongated fibres of suspensory ligament clearly seen.

IV 25. J. W., aged 14 years. Normal eyes.

IV 26. S. W., aged 11 years. Marked photophobia in bright light. Blue sclerotics present.

R. eye :—No iris present. Lens dislocated upwards. Lens clear but fundus difficult to see because of ? tilting of lens. Disc clearly seen through aphakic part of eye: fundus appears normal. Tension + +. Vision—6/36. Mixed astigmatism present. Sees J.14, holding print very closely to eye.

L. eye :—No iris present. Lens dislocated upwards as in R. eye, clear and slightly tilted. Aphakic portion clear, but disc difficult to see because of intervention of rim of lens. Tension + +. Vision—6/60, but improves to 6/36 with -2·50 D. cyl. at 180°. A mixed astigmatism is present, but the + constituent is not accepted. Vision is not improved on either side by correction of the aphakia. Sees J.14.

IV 27. J. W., aged 7 years. Schoolgirl.

R. eye :—Complete aniridia. Lens dislocated upwards. Lens and vitreous clear. An atrophic and cupped disc present, with no central vessels but all emerging from periphery of disc. Tension + +. Vision—6/60 and J.16, held very close. Mixed astigmatism present.

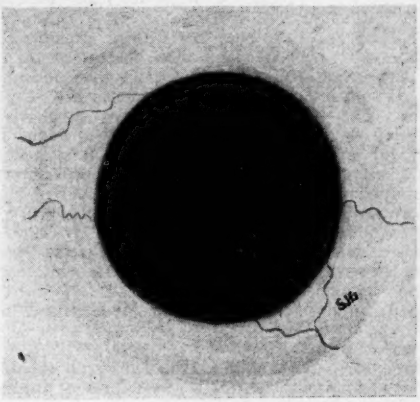
L. eye :—Complete aniridia. Lens clear, but dislocated upwards. L. fundus healthy. Tension +. Vision—6/36 and J.16. Vision not improved by correction (mixed astigmatism).

With the slit-lamp the elongated fibres of the suspensory ligament on each side could be seen very irregularly disposed and with a wedged shaped gap between 5.30 and 6.30 o'clock, suggestive of colobomata. The vitreous beyond was fluid and degenerate. A needling of R. lens was recently performed. This was followed by a lowering of intra-ocular tension, except for a transient rise lasting one day. The lens is now in process of absorption.

IV 28. W. W., aged 3 years. Normal eyes.
IV 29. Normal eyes.
IV 30-43. Normal eyes.
IV 44. G. W. T., aged 40 years. Is a carman. This man has no children, so that his genetic potentialities are not known.

R. eye :—Partial coloboma of iris present at 9 o'clock. Several areas of hypoplasia of stroma showing deeper pigmented layers in base of gaps. Some proliferation of posterior pigmented layers present in region of coloboma. One long strand of persistent pupillary membrane present. Lens and fundus normal. Vision—6/5.

L. eye :—Partial coloboma at 4.30 o'clock. Four small areas of hypoplasia of stroma, showing pigmented posterior layers of iris. One small area at 5.30 o'clock in which all layers of iris are absent and a good red reflex can be seen. Some



IV 45. Mrs. M. S. Left eye by focal illumination.

proliferation of posterior pigmented layers in region of coloboma. Lens and fundus—normal. Vision—6/6.

IV 45. Mrs. M. S., aged 38 years. This woman's eyes at a casual glance would pass for normal.

R. eye :—Normal except for a gap in the superficial stroma and proliferation of deeper pigmented layers at the pupillary margin, between 7-9 o'clock. Lens and fundus—normal. Vision—6/5.

L. eye :—A small area of hypoplasia of iris stroma at 6 o'clock, showing deeper pigmented layers. A few strands of stroma can be seen passing over the area. Three other smaller such areas are present in the lower temporal region. At the pupillary margin the stroma is deficient from 4-9 o'clock, with proliferation of posterior pigmentary layer. Lens and fundus—normal. Vision—6/12.

IV 46. Mrs. B. Normal eyes.

IV 47. Mr. J. T., aged 32 years. This man works in a sand-pit.

R. eye :—Cornea normal. A thin fringe of iris extends from 7.30 to 5 o'clock, with an area from 5 to 7.30 o'clock; completely without iris. The lens has a superficial paracentral opacity just below anterior capsule, and a deep opacity in the lower nasal quadrant. Fundi—normal. Tension—normal. Vision—6/36 with correction (+6·00 D. sphere) improves to 6/12.

L. eye :—Same distribution of iris as in the right eye. Deep lens opacity present in lower temporal quadrant. Fundus—normal. Tension—normal. Vision—6/36, with correction (+6·00 D. sphere) improves to 6/12.

There may be some impairment of accommodation present here, as he sees to read very much better with +7·00 D. The extra dioptre considerably impairs his distant vision.

IV 48. Mr. E. W. Normal eyes. Was a driver in the army.

IV 49-56. Normal eyes.

IV 57. Mr. W. R. This man is a lorry driver by trade. Was passed A1 for army and accepted for railway work.

R. eye :—Partial coloboma of iris down and out, with proliferation of pigmented posterior layers to fill the gap. Six small areas of localized hypoplasia of iris stroma. Lens and fundus—normal.

L. eye :—Partial coloboma of iris down and out, with same pigmentary proliferation as on R. side. Four areas of hypoplasia here in lower temporal quadrant. Lens and fundus—normal.

This man is not married and therefore his genetic potentialities are not known

IV 58. Mrs. E. R., aged 30 years. Housewife. Sees well. Slight discomfort in bright light.

R. eye :—Small fringe of pale blue iris present extending from 10 30 to 4 o'clock, with notch at 1 o'clock. Lens not dislocated. A very faint central capsular opacity, with several flecks of thicker opacity present in inferior quadrants. Tension—normal. Fundus shows some small patches of old choroiditis in upper temporal quadrant. The anterior capsule of lens is flecked with numerous fragments of pigment, the usual legacy of an attack of iritis.

L. eye :—Fringe of iris extending from 8 to 1.30 o'clock. A slight central anterior capsular opacity present. Fundus and Tension—normal.

IV 59-75. All normal eyes.

V1 and V2. Normal eyes.

V3 D. W., aged 2 years.

R. eye :—complete aniridia. Lens is completely clear: equator of lens can be seen all round. Fundus appears normal, but disc and macular area difficult to see on account of child's restlessness.

L. eye :—As on R. side. A slight central opacity is present on anterior capsule of lens.

V4-7. Normal eyes.

V8. M. S., aged 4 years. This child is troubled by photophobia in bright light. She has a R. convergent squint, which has been present for two years.

R. eye :—Iris present, though narrower than normal iris and with a crenated pupillary margin, between 7.30 p.m. and 5 o'clock. Lens is not dislocated, but lower edge can be seen below. Fundus—normal. Vessels tortuous.

L. eye :—Large coloboma iris between 5.30 and 7 p.m. Lens in normal position and lower edge visible.

Precise vision not determined: each eye has a refractive error of +3·50 D. sph. and +1·00 D. cyl. at 90°

V9-V20. Normal eyes.

I am very much indebted to Mr. Esmond Recordon for introducing me to this family and for his generous encouragement and advice. Dr. R. R. Race very kindly did the blood examinations.

REFERENCES

1. BELL, JULIA (1932).—Treasury of Human Inheritance, Vol. II, Part V.
2. ——(1934).—*Nature*, Vol. CXXXIII.
3. RISLEY, S. D.—Hereditary Aniridia. 'An Interesting Family History. *Jl. Amer. Med. Assoc.*, Vol. LXIV, 1915.
4. DUKE-ELDER, W. S.—Text-book of Ophthalmology, Vol. II, p. 1300.
5. FOSTER, M. L.—Congenital Irideremia. *Arch. of Ophthal.*, Vol. XXVII, pp. 593-615, New York, 1898.
6. WAARDENBURG, P. J.—Modern Trends in Ophthalmology (Ridley and Sorsby), p. 119, 1940.

7. CORNER, G. W. (1944).—Ourselves Unborn. Terry Lectures. Yale University Press, p. 99.
8. COCKAYNE, E. A. (1933).—Inherited Abnormalities of the Skin, p. 32.
9. MANN, IDA.—*Trans. Ophthal. Soc. U.K.*, Vol. LIII, 1933.
10. STEPHENSON, S.—Irideremia in Two Brothers. *Trans. Ophthal. Soc., U.K.*, Vol. XVI, London, 1896.
11. DRINKWATER.—Quoted by Julia Bell. Treasury of Human Inheritance. Vol. II, part V, p. 530 (no original article).
12. SHRÖTER, P. Quoted by Julia Bell. Treasury of Human Inheritance. Vol. II, part V, p. 526.
13. COCKAYNE, E. A. (1933).—Inherited Abnormalities of the Skin, p. 31.
14. HALDANE, J. B. S. (1935).—The Rate of Spontaneous Mutation of a Human Gene. *Journal of Genetics*, Vol. XXXI, pp. 317-326.
15. MOLLENBACH (1944).—" Mutation as a Cause of Disease." *Acta Path. et Micro. Scand.*, Supp. 54. Article by Tage Kemp.
16. COCKAYNE, E. A. (1933).—Inherited Abnormalities of the Skin, p. 35.
17. WAARDENBURG, P. J. (1940).—Modern Trends in Ophthalmology (Ridley and Sorsby), p. 102.
18. BAUR, FISCHER and LENZ.—Human Heredity, p. 241.
19. FRASER ROBERTS.—Introduction to Medical Genetics.
20. CORNER, G. W. (1944).—Ourselves unborn. Terry Lectures. Yale University Press, p. 110.
21. COLLINS, TREACHER (1893).—*Trans. Ophthal. Soc. U.K.*, Vol XIII, p. 128.
22. MANN, IDA (1937).—Developmental Abnormalities of the Eye, p. 240.
23. ——— (1924).—Coloboma Iridis and its Embryology. *Trans. Ophthal. Soc. U.K.*, Vol. XLIV.
24. ——— (1937).—Developmental Abnormalities of the Eye. P. 244.
25. CORNER, G. W. (1944).—Ourselves unborn. Terry Lectures. Yale University Press, p. 104.
26. MANN, IDA (1935).—*Glas Med. Jl.*, Vol. CXXIV, p. 64.
27. COATS, GEORGE (1910).—*Ophthalmoscope*, Vol. VIII, p. 706.
28. COLLINS TREACHER.—*Trans. Ophthal. Soc. U.K.*, Vol. XIII, p. 133.
29. DUKE-ELDER, W. S.—Text-book of Ophthalmology, Vol. II, p. 1300.
30. LINBERG, J. G.—Treasury of Human Inheritance, Vol. II, Pt. V (Julia Bell), p. 531, and Holm's Case, p. 528.
31. LICSKO, A. (1927).—Treasury of Human Inheritance (Julia Bell), Vol. II, Pt. V, p 524.
32. THEOBALD, S. (1888).—Treasury of Human Inheritance (Julia Bell), Vol. II, Pt. V, p. 525.
33. DE BECK, D. (1897).—A Family History of Irideremia and Coloboma Iridis. *Trans. Amer. Ophthal. Soc.*, Vol. VII.
34. CROSS, F. R (1895).—Congenital Anomalies of Iris. Clinical Sketches, Vol. I, pp. 104-106.
35. POLTE, L. (1908).—Several Cases of Congenital Anomaly of the Iris. *Arch of Ophthal.*, Vol. XXXIII.
36. SNELL, S. (1908).—Coloboma of Iris in Each Eye Occurring in Five Generations. *Trans. Ophthal. Soc. U.K* , Vol. XXVIII.
37. WAARDENBURG, P. J. (1919).—Treasury of Human Inheritance (Julia Bell), p. 532.
38. HAMILTON, T. K. (1905).—A Family with Irideremia. *Ophthalmoscope*, Vol. II, pp. 481-488.
39. HOLM, E. (1921).—Treasury of Human Inheritance (Julia Bell), Vol. II, Part V, p. 528.
40. ALGER, L. G. (1945).—*Amer. Jl. Ophthal.*, Vol. XXVIII, pp. 730-735.
41. NUNNELEY, T. (1861).—Congenital Malformation of Eyes in Three Children of One Family. *Lancet*, Vol. II, pp. 569-570.
42. NUNNELEY, J. A. (1877).—Cases of Irideremia Totalis. *Lancet*, p. 754.
43. BELL, JULIA (1932).—Treasury of Human Inheritance, Vol. II, Pt V, p. 470.
44. COLLINS, TREACHER.—*Ophthal. Rev.*, Vol. X, p. 161.
45. JULER, H. (1902).—Aniridia. *Ophthal. Rev.*, Vol. XXI, pp. 22-23.
46. BROOK-LEWIS, J. (1926).—Aniridia in Four Generations. *Med. Jl. of Australia*, Vol. I, p. 489.

47. BLAIR, C. and POTTER, B. (1903).—Two Cases of Aniridia and one of Coloboma of the Iris in the same Family. *Trans. Ophthal. Soc. U.K.*, Vol. XXIII.
48. CLAPP, C. A. (1944).—*Amer. Jl. of Ophthal.*, Vol. XXVII, No. 7. (Included in Collected Reprints of Wilmer Institute of Ophthalmology).
49. BATTEN, RAYNER (1900).—Congenital Aniridia and Displacement of Lenses with Glaucoma. *Trans. Ophthal. Soc. U.K.*, Vol. XX, p. 192.
50. MOHR, W. (1895).—Treasury of Human Inheritance (Julia Bell), Vol. II, Pt. V, p. 527.
51. VELHAGEN, C. (1923).—Treasury of Human Inheritance (Julia Bell), Vol. II, Pt. V, p. 532.
52. TIFFANY, F. B. (1900).—*Jl. of Amer. Med. Assoc.*, Vol. XXXIV, pp. 1043-1044.
53. PAGE, H. (1874).—Transmission through Three Generations of Microphthalmos, Irideremia and Nystagmus. *Lancet*, Vol II, p. 193.
54. BENSON, A. H. (1878).—Congenital Irideremia of Both Eyes. *Brit. Med. Jl.*, Vol. II, p. 359.
55. REID, A. MCKIE (1938).—Case of Congenital Aniridia fitted with Pigmented Contact Glasses. *Trans. Ophthal. Soc. U.K.*, Vol. LVIII, p. 434.
56. WEINER and ALVIS (1939).—Surgery of the Eye. P. 134.
57. HUDSON, A. C. (1921).—*Trans. Ophthal. Soc. U.K.*, Vol. XLI, p. 274.
58. GIFFORD, S. (1926).—Congenital Aniridia. *Amer. Jl. Ophthal.*, Vol. IX, 1924.

INDUCTION OF AN EXPERIMENTAL TUMOUR OF THE LENS*

BY

IDA MANN

LONDON

IT is a curious fact, hitherto ignored by pathologists, that neoplasms of the lens are unknown to ophthalmologists. It is often stated by students of cancer that any tissue or organ capable of cell division may be the site of a malignant neoplasm, yet the lens, as far as we know, in spite of the fact that mitoses occur in the subcapsular epithelium throughout life, never produces a cancer. This immunity may theoretically be due to various causes. It might be that the cells of the lens vesicle are inherently from the beginning resistant to malignant change. This would be strange since, if it were true, the lens would stand practically in a class by itself. It might also be that the presence of the capsule inhibits new growths of the lens, either by the tension it exerts or by its properties of a semipermeable membrane, preventing access of the required stimulus to the lens cells. That this is not the case is obvious, since lenses with ruptured capsules never become malignant. A third possibility is that the lens owes its immunity

* Paper read before the Ophthalmological Society of the United Kingdom, Glasgow, March 27, 1947.

to its lack of blood supply. This presupposes the possibility of a blood borne cause of cancer. It would therefore seem of interest both ophthalmologically and pathologically to discover whether the cells of the subcapsular epithelium (the only ones capable of dividing after birth) could be induced experimentally to undergo malignant change.

Pathological techniques for the induction of experimental cancer include the use of chemical carcinogenetic agents and the investigation of inbred strains of animals. By a combination of these methods applied to the lens it can be shown that, when treated with a chemical carcinogen *and* provided with a blood supply the subcapsular epithelium will produce an epithelioma of extreme malignancy. There is, therefore, no inherent intracellular immunity of the lens to cancer and it is likely that its escape is due to its avascularity. The chemical agent chosen for the experiments was methylcholanthrene. This is known to induce tumours in many species of mammals (including rabbits and mice) when a minute quantity of it is placed in or in contact with the organ under investigation. Some strains, even of the same species of animal, are more resistant than others to this agent and in all species there is a latent interval of weeks, months or years (according to average length of life) before the tumours appear.

The first experiments were done on rabbits. A droplet of 0·4 per cent. solution of methylcholanthrene in liquid paraffin was injected with a fine needle into the lens cortex. The minute puncture of the capsule sealed completely and the lens remained clear, so that slit-lamp observation was possible. The oil could be seen lying in globules along the needle track. It showed a purple fluorescence in the slit-lamp beam, owing to the presence of the methylcholanthrene. The eyes were observed at weekly and then monthly intervals for 10 months, but no change in the lens occurred. Transparency was maintained and the droplets did not change their position in the lens, though a few minute crystals separated out within them. The eyes remained quiet throughout. It is possible that the animals have not yet been observed sufficiently long, but so far no effect has been produced by injecting the lens *in situ*.

It therefore seemed advisable to attempt to transfer the lens to a position where it could acquire a blood supply and there to treat it with the methylcholanthrene. For this purpose inbred strains of animals are necessary, and mice were chosen, both for their relative rapidity of reaction and because inbred strains showing a high natural cancer incidence were available.

Homozygous strains of mice are produced from a single pair by brother-sister matings through many (at least 30 and preferably

100) generations. When successful this inbreeding produces a pure strain in which all the mice resemble each other, all react in the same way to the same stimuli and all can be grafted with tissues (both normal and malignant) from each other without the production of immunological reactions leading to the death of the graft. Many of these strains exist and one of them, the C3H strain, was chosen as it was naturally prone to develop cancer and was known to react readily to methylcholanthrene.

The method was suggested by the work of Peyton Rous and Smith[1], who showed that when embryo tissue of pure line strains was grafted intramuscularly in adult related mice together with a trace of methylcholanthrene, malignant teratomas developed. These could be maintained indefinitely by transplantation from mouse to mouse of the same strain.

The lenses were dissected out from the eyes of young mice and implanted with the carcinogen under the skin of the flank of adult related mice. Three cancers of subcapsular epithelium were obtained.

Experiments and details of technique

Thirty-eight experiments were performed and 26 tumours resulted. Of these, three were carcinomas of the subcapsular epithelium and the remainder various types of sarcoma of the host mouse or epitheliomas of its skin. The three lens tumours occurred in the subcutaneous tissue of the flank of male mice, which rules out any possibility of derivation from mammary gland tissue of the host. The lenses were obtained from the eyes of mice of various ages (new born, two days, three days, four days, seven days and nine days old), but tumours were induced only with seven day and nine day old lenses. They were inserted under the skin of the flank of mice of the same inbred strain, together with methylcholanthrene. In some cases the hyaline capsules were ruptured and the lenses mixed with a few crystals of methylcholanthrene. In others the unruptured lenses coated with a solution of the carcinogen in oil were used. In others again teased lenses were mixed with methylcholanthrene in solution in equal parts of soft and liquid paraffin. The exact method employed did not appear to be important, two of the tumours being obtained with a solution of 1 mg. of methylcholanthrene per 0·5 c.c. of a mixture of soft and liquid paraffin, and the third tumour with crystals only. In all the successful experiments the lens capsules were ruptured. The tumours appeared between two and three months after implantation.

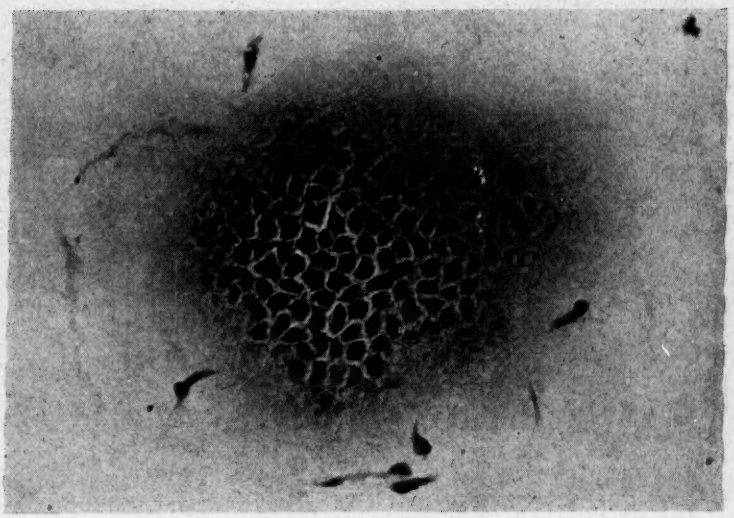


FIG. 1.

Tangential section through the subcapsular epithelium of the mouse lens at the anterior pole.

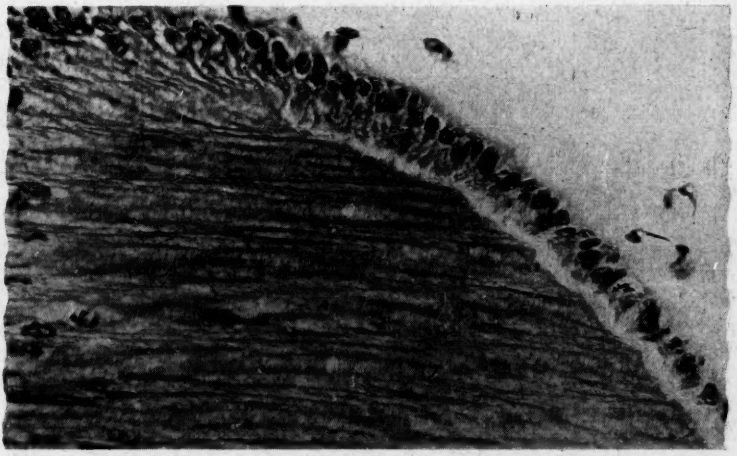


FIG. 2.

Subcapsular epithelium and equatorial region of lens of seven day old mouse.

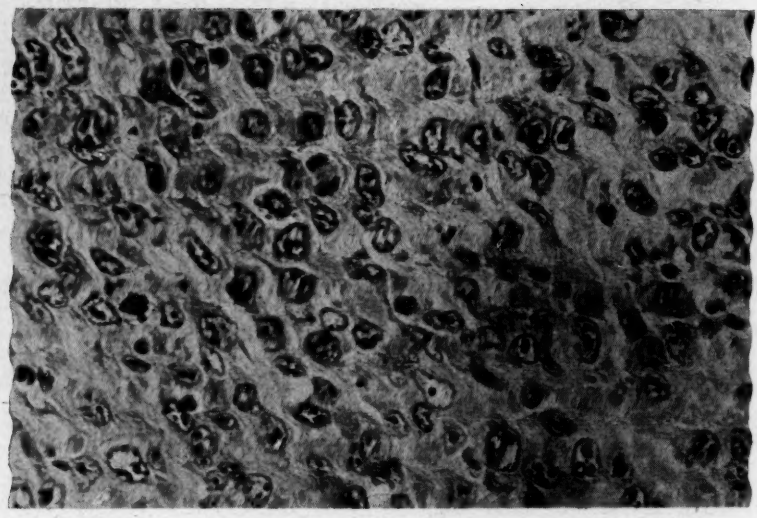


FIG 3.

Section through lens tumour. Nuclei showing mitosis and typical arrangement of chromatin.

The tumours obtained were anaplastic carcinomas possessing certain characteristics of structure suggestive of their origin from the subcapsular epithelium (Figs. 1 and 3). They were investigated by stained sections, by smear preparations, by passaging them through other mice of the same strain and by observing their behaviour in tissue culture.

The first tumour obtained (known as M8.134) can be taken as the type and described in full.

Protocol of experiment M8.134

The lens of a seven day old C3H mouse was mixed with a 0·2 per cent. solution of methylcholanthrene in equal parts of soft and liquid paraffin and inoculated into the subcutaneous tissues of the right flank of a male C3H mouse one month old. The small lump resulting from the inoculation remained for three—four weeks and finally disappeared. A tumour appeared at the site fairly suddenly about two and a half months after inoculation and grew rapidly, being ready for transplantation a fortnight later. The mouse was killed and the tumour examined and transplanted into six C3H mice. It has retained its characteristics through eight

passages so far and continues to grow rapidly, no failure being noted in any of the transplants.

Characteristics of lens tumour M8.134.—The tumour tissue is greyish and translucent. The grafts grow rapidly and form large tumours filled with necrotic tissue and blood. Sections of the periphery of the tumour show large cells with voluminous or oval

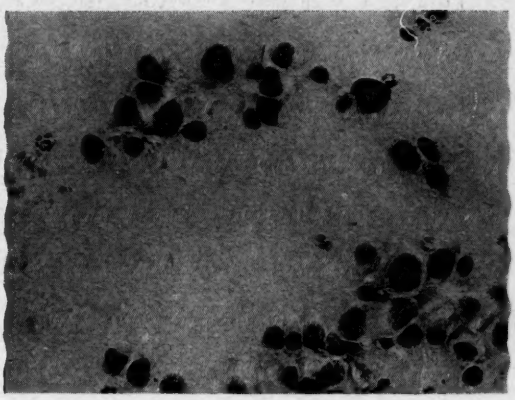


FIG. 4.

Smear preparation of lens tumour. The typical chromatin arrangement and the displacement of some of the nuclei to one side can be seen.

FIG. 5.

Tissue culture of lens tumour at 48 hours. Living preparation.

nuclei, prominent nucleoli and a reticular or punctate arrangement of chromatin. They resemble the normal cells seen in Fig. 1. Mitoses are frequent. In the young cells the nucleus is central, in the older cells it moves to the edge of the cell just before becoming pyknotic, as does the nucleus of the normal subcapsular epithelial cell before it differentiates into a lens fibre (Fig. 2). Large areas of necrosis and liquefaction occur in the centre of the tumour. Metastases occurring in the inguinal lymph nodes show the same

FIG. 6.

Extending flat sheet of cells at edge of tissue culture of living lens tumour at four days.

structure, but with less necrosis. The tumour is soft and the cells can be well seen in smear preparations (Fig. 4).

The tumour was grown in tissue culture* and Figs. 5, 6 and 7 show some results. Fig. 5 shows the explant after 48 hours. Tumour cells and a few fibroblasts are beginning to wander out. By four days (Fig. 6) the tumour cells have arranged themselves in the flat sheet typical of tissue cultures of carcinomas, as distinct from sarcomas, which show a scattered arrangement. If the culture is continued the sheet of cells tends to break away from the tumour explant and large and small islands of cells float free in the medium. Fig. 7 shows this and also demonstrates clearly the epithelial character of the cells. A high power photomicrograph of a portion of the sheet in Fig. 7 is seen in Fig. 8. The preparation is fixed and stained. Mitotic figures and completed mitoses are

* The best medium was found to be one part of rat serum, two parts tyrode solution and one part mouse embryo extract. Sometimes a few drops of distilled water were added.

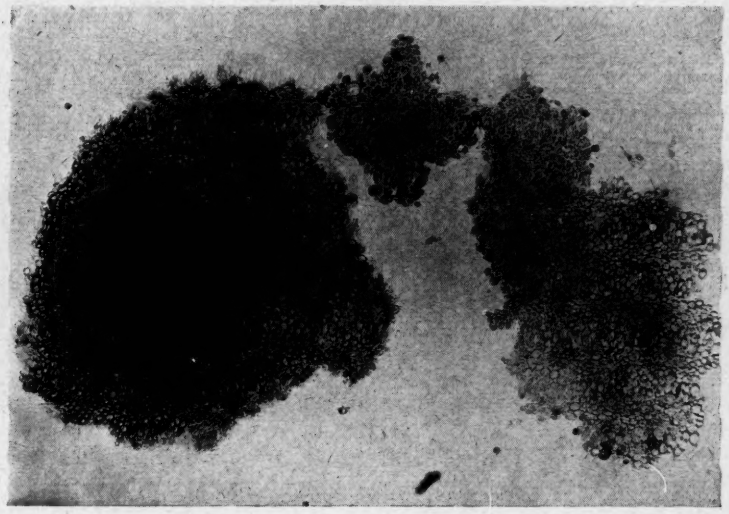


FIG. 7.

Five day tissue culture of lens tumour M8. 134. The explant is on the left, the new sheets of cells are breaking away on the right. Living preparation.

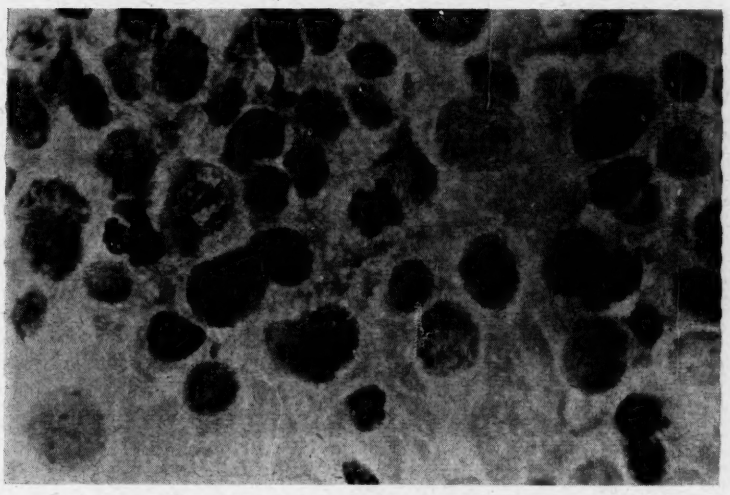


FIG. 8.

Fixed and stained preparation of five day tissue culture of tumour M8. 134. Note characteristic nuclei and presence of mitotic figures.

seen. The similarity of the cells to those of the tumour seen in Figs. 3 and 4 is apparent. In some of the tissue cultures of the tumour the extending edge showed fibrillar outgrowths somewhat similar to those described by Kirby[2] in tissue cultures of chick lenses. These are seen in Fig. 9. This fixed preparation of a five day tissue culture of the same tumour also demonstrates the attempted differentiation by movement of the nucleus to the side of the cell before pyknosis sets in.

The other two tumours resembled M8.134 in their structure and behaviour. They were slightly slower in growth and one of them, although showing the same characteristic epithelial cells, also contained sarcomatous areas, probably derived from the host.

The main points which show these tumours to be derived from the implanted lens epithelium are their carcinomatous character, their growth in tissue culture in friable sheets and the displacement of the nuclei and their degeneration in the course of attempted differentiation.

Since these tumours are derived from the lens epithelium which is the anlage of the lens fibres, one might expect them to resemble these somewhat in chemical composition and therefore to contain

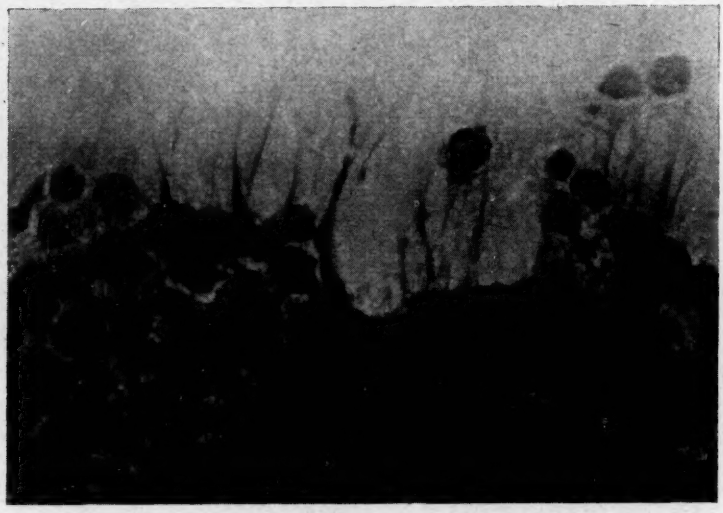


FIG. 9.

Growing edge of five day tissue culture of lens tumour M8. 134 showing fibrillar processes from the cells and the attempt at differentiation shown by the movement of the nucleus to the side of the cell. Some of these displaced nuclei are pyknotic.

the organ specific protein α crystallin. Although this is by no means the only protein in the adult lens, its universal presence has led to the idea that the lens, unlike all other organs, has very little or no species specificity. If this were true (which is doubtful) these lens tumours might be expected to grow when grafted into other strains of mice, or even into other species of animals. Experiments to decide whether this was the case were therefore undertaken. The tumours, being known to grow well when grafted into mice of the same homozygous strain, were grafted into mice of other inbred strains, some showing a high and some a low incidence of spontaneous cancer. The high cancer lines, Strong 3 and R3 and the low, C57 black and the S strain, were used. The tumour failed to grow in all of these. It is not, therefore, even chemically common to mice as a whole.

The work of Greene[3] on the growth of heterologous tumours in the anterior chamber of the rabbit's eye suggested that the mouse lens tumour might be tried in this way. Two of the three lens tumours were planted out on to the iris of rabbits, and the course of events carefully watched with a slit-lamp. A slight inflammatory reaction occurred around the tumour, shown by a gelatinous exudate and a few haemorrhages. The graft then shrank, became buried by the iris stroma and disappeared. In 10 days its site was only apparent as a small puckered scar-like area on an otherwise normal iris. Lens tumours do not, therefore, exhibit organ specificity.

In conclusion I wish to thank the Council of the Imperial Cancer Research Fund for their assistance in this research.

Summary

The statement has been made by general pathologists that any tissue or organ capable of cell division may be the site of a malignant neoplasm. Ophthalmologists, however, agree that carcinoma of the lens is unknown, although mitoses occur in the lens epithelium throughout life. The possible reasons for this are discussed. Experiments showing the induction of cancer of the lens in mice are described, using pure line strains and chemical carcinogens. These demonstrate the ability of the lens epithelium to become malignant under certain conditions, and throw some light on the immunity of the organ in the body.

BIBLIOGRAPHY

1. ROUS, PEYTON, and SMITH, WILLIAM E.—The neoplastic potentialities of mouse embryo tissues. *Journ. Exper. Med.*, Vol. LXXXI, 6, June 1, 1945, p.p. 597-645.
2. KIRBY, DANIEL B.—A study of the nutrition of the crystalline lens. *Trans. Am. Acad. of Ophth., Otolaryngol.*, 1926, p. 137.
3. GREENE, H. S. N.—Heterologous Transplantation of Mammalian Tumours, *Jl. Exp. Med.*, Vol. LXXIII, pp. 461-468, 1941.

XANTHELASMATA AND AUTONOMIC NERVOUS SYSTEM. A NEW SYNDROME*

BY

A. BAKKER

GRONINGEN

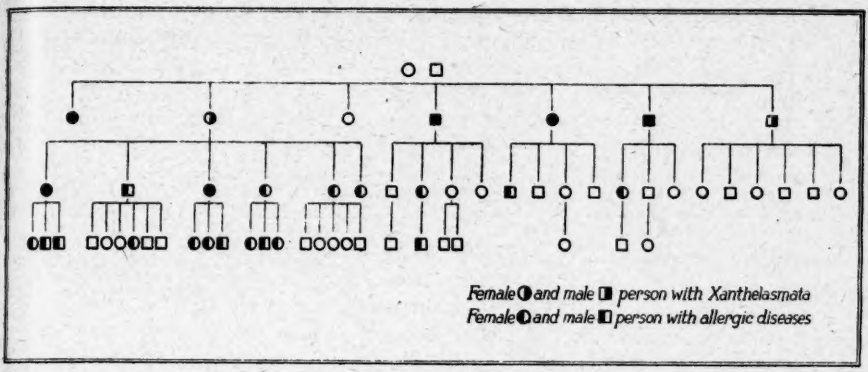
THE common opinion on xanthelasmata is that these small tumours, which are hardly elevated above the level of the skin, are produced by local degenerative processes.[1] Predilection place is the skin of the eye-lids. They are quite harmless; the only trouble they cause is a slight disfigurement of the face, which, however, evidently does not disturb everyone. At least, I know ladies who were not aware of the fact that they were bearers of these tumours. Generally these new growths are only mentioned casually and it does not often occur that patients call on an oculist expressly for the purpose of getting rid of them.

When one's attention is fixed on the existence of these tumours, one gets the impression that they occur more frequently than one originally expected. The reason that I am giving special attention to the xanthelasmata is the accidental circumstance that I had to treat several members of one family who were not only bearers of these tumours, but were also suffering from various kinds of allergic diseases, such as asthma, hay fever, urticaria, eczema and migraine (see pedigree).

When patients with xanthelasmata are carefully interrogated, they, themselves, show almost without any exception one or more types of allergy and, if they do not, other members of the family do. However, it is necessary to interrogate all these members personally, as it often occurs that for instance one sister does not know that her other sister has xanthelasmata or allergic symptoms. The following case gives a good picture of the intimate relation which exists between the apparently different kinds of these diseases in one family. A lady with xanthelasmata gets urticaria after eating strawberries or after taking aspirin. In two of her sisters urticaria breaks out after contact with a primula obconica. Another sister has hay fever. A son of her mother's brother is suffering from allergic asthma.

I have not sufficient statistic material at my disposal, thus I am not quite certain, but I got the impression that also an arcus senilis often occurs simultaneously with xanthelasmata at a relatively early age.

* Received for publication, March 25, 1947.



We may say that the frequency of the above mentioned allergic diseases is rather great, but doubtlessly not so great that it can give an explanation for the simultaneousness of xanthelasmata and allergic disorders.

From the pedigree it is visible that the inheritance of the allergic symptoms is of a dominant character. Of the great-grandmother and the great-grandfather no peculiarities were available. Four of the seven children of these ancestors show the syndrome (the third child died at a relatively early age). The remaining six children, all still living, have xanthelasmata. Unfortunately I had not the occasion to examine nor to interrogate the offspring of the seventh child and thus I am not certain that these individuals have really no symptoms at all. The same can be said of the five children in the youngest generation, whose parents wrote me that they are unaffected. Among the members of the third generation we only find two persons with xanthelasmata. This is, however, not astonishing, because most of them have not yet reached the age at which these tumours generally appear.

It was striking to observe that many of the patients with xanthelasmata had a labile autonomic nervous system and this may perhaps supply the key to the obscure secret which envelops the relation between the xanthelasmata and the allergic disorders. It is a well known fact that also allergic patients often show various kinds of dysfunction of the vegetative nervous system. One of the male representatives (aged 45 years) in my pedigree possessed a whole series of these symptoms, such as hyperhidrosis, an infantile respiratory arrhythmic pulse, cold feet, blushing and other vasomotor disorders and spastic constipation.

If we now ask the question whether there is anything known of the influence of the sympathetic or para-sympathetic nerves on the

developing of xanthelasmata we must answer that little or nothing is known of it. These tumours are built up by large, epithelium-like cells with spongy protoplasm. These cells contain large quantities of neutral fat and cholesterol. Corresponding to the above described close relation which exists between these tumours and more generally determined somatic disorders, it seems quite improbable that the aetiology of xanthelasmata must be looked for exclusively in local degenerative processes. Also the results of several investigators who noticed a hypercholesterolemia in these patients is not in accordance with the latter opinion. Certainly, not every bearer of xanthelasmata shows an increased concentration of cholesterol in the blood, but this does not prove that in some period of his life he has not had it. Furthermore we must pay attention to the ratio of free cholesterol and its esters with unsaturated fatty acids. This ratio seems to be of especially great importance and a disturbance of this normal ratio we could call dyscholesterolemia.

Our knowledge in questions of fat and lipoid metabolism is rather defective. Cholesterol in every respect is a curious substance. We may say that generally the animal organism is not able to synthesize cyclic products (acyclopoiesis), but the cholesterolsynthese is an undeniable fact. Nevertheless, a large fraction of the required cholesterol is taken in with our food. Before the resorption in the intestine can take place both fats and lipoids have to undergo phosphorylation. The investigations of Verzár[2] have shown that corticosterone katalyzes the processes of phosphorylation and here, perhaps, we have the connecting link between the autonomic nervous system and the cholesterol metabolism. Experiments of de Langen[3] probably point to the same direction. Hyperlipaemia in rabbits was caused by artificially provoked anaemia. No hyperlipaemia developed when the spinal cord between the third and fourth thoracic vertebrae was cut.

It would be of great interest to know more about the fluctuations in the cholesterol concentration in the blood of patients with xanthelasmata and this especially during long periods of their life. Likewise it would be useful to have more information on the lipoid metabolism in patients with allergic diseases. But as far as I know there are no investigations dealing with this subject. Theoretically we must finally take into account the possibility that an increased cholesterol content of the blood has influence on the tonus of the sympathetic and para-sympathetic nerves and the result of this could be a hypersensitivity for substances such as albumen, pollen, strawberries and so on.

Summary

Almost without exception patients with xanthelasmata suffer from various kinds of allergic diseases, and if they do not, at any rate we find allergic disorders in their relations. As these benign tumours are probably closely related to the cholesterol metabolism and the latter stands under the regulating influence of the autonomic nervous system and as finally allergic disorders have much to do with the sympathetic and the para-sympathetic nerves, an attempt is made to consider all these apparently heterogeneous diseases from one viewpoint, *i.e.*, a dysfunction of the vegetative nervous system.

REFERENCES

1. DUKE-ELDER.—Text-book of Ophthalmology. Vol. II, p. 1437.
2. VERZÁR, F.—*Lehrb. der spez. Path. Physiol.*, p. 388, third edition.
3. DE LANGEN, C.—*Acta Med. Scandinavica*, Vol. XCVII, p. 427, 1938.

A CASE OF BILATERAL COLOBOMA OF THE *OPTIC DISC**

BY

H. L. HUGHES.

LONDON

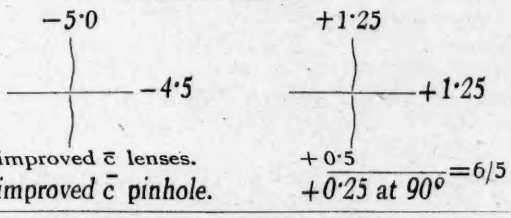
Report of a Case

THE patient, Patrick N., aged 24 years, presented with the complaint that his right eye had turned outwards since an injury when he was only a few months old. It had not troubled him until he contemplated marriage and he came to ask for a cosmetic operation. (The patient was demonstrated at the May, 1947, meeting of the Section of Ophthalmology, Royal Society of Medicine).

Family history and past medical history: essentially irrelevant.

Examination. Vision: Right eye P.L. only. Left eye 6/6.

Under H. and C.



* Received for publication, July 2, 1947.

The right eye shows a divergent strabismus with an angle of 40°. The eye movements are full, but the patient cannot fix with the right eye. There is no nystagmus. The eyes are of normal size. The pupils are round, regular, equal and react to light and accommodation. The right pupil reacts more sluggishly than the left.

The right cornea shows evidence of past inflammation in the form of both superficial and deep vessels. The left cornea is clear.

Ophthalmoscopic Examination, Figs. 1 and 2.

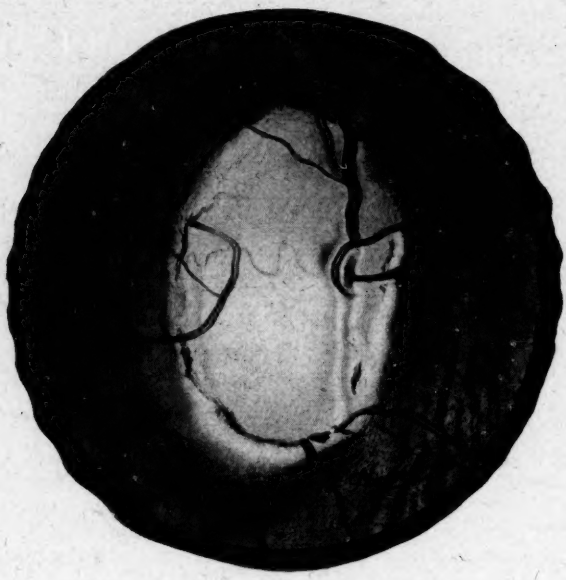


FIG. 1.

Right eye. The most striking part of the fundus picture is the pseudo-optic disc which appears to be two and a half times the normal size. It is deeply cupped and of a dead white pallor.

The upper half is rounded and well outlined and contains a rim of pink nerve tissue. The lower half is deeply cupped. The retinal level at the lower border of the disc is seen with a −1·0 D. whilst the floor of the cup may be defined with −18·0 D. The entire pseudo-disc is bordered by scattered pigment and on the nasal side is a white scleral ring.

The vessels in the upper half of the disc emerge from the pink nerve tissue within the disc surface, whilst below they dip over the steep edge of the cup and are lost to view.

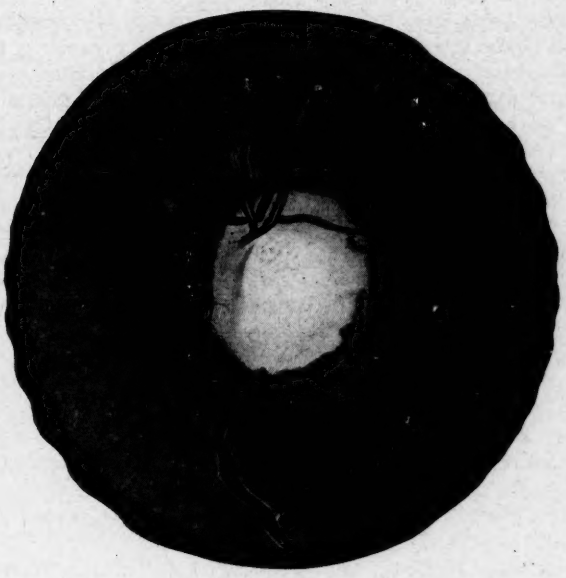


FIG. 2.

Left eye. The condition is similar but not as marked. The retinal level at the lower border of the disc is seen best with +0·5 D. and the floor of the cup with −6·0 D. The vessels behave like those in the other eye. The intra-ocular tension is:—

Right 20 mms. } Schiötz
Left 22 mms. }

There is a suggestion of a crater-like hole at 2 o'clock.

General examination revealed no other developmental abnormalities.

Discussion

The case is presented as an addition to the 50 odd cases recorded and recently reviewed by Steinberg of San Francisco.

The condition is usually unilateral when vision may be normal but is more often seriously defective. Bilateral cases have been *recorded by Adler, Calhoun, Johns, and more recently by Magnus.* In such cases one eye is usually blind whilst the vision in the other *is nearly normal.*

The most generally accepted theory of pathogenesis is that of *von Ammon—"defective closure of the optic cup in its extreme* posterior position. Associated is an abnormal development of the

surrounding mesoderm (precursor of choroid and sclera) with a later extension of the resulting scar tissue."

Johns offered as explanation a failure in development of the papillo-macular bundle the fibres of which would normally occupy the area of the cup. Such an explanation is inconsistent with vision such as that of the present patient, *i.e.* 6/5 (left).

The classification of such cases usually follows that given by Caspar who described three groups.

(1) Cases in which all the vessels are coming from the lower portion of the pseudo-disc, even those which later turn upwards.

(2) Cases in which vessels emerge at or a little above the centre—their arrangement being almost normal.

(3) Cases in which the vessels appear at the circumference of the disc and appear to bend sharply around its edges.

The present case falls into the third group. The diagnostic features are: (1) Enormous size of disc, or what corresponds to disc. (2) Deep cup. (3) Dead white pallor.

The differential diagnosis must include for completeness: (1) Glaucomatous cupping. (2) Cavernous optic atrophy.

The first is excluded by a study of tension and fields. The latter occurs at a much later period.

I am indebted to Prof. Arnold Sorsby for the diagnosis of this case.

REFERENCES

ADLER, F. H. (1937).—*Amer. Jl. Ophthal.*, Vol. XX, p. 777.
CALHOUN, F. P. (1930).—*Arch. of Ophthal.*, Vol. III, p. 71.
CASPAR, J. H. (1887).—Cited by Steinberg.
JOHNS, J. P. (1930).—*Amer. Jl. Ophthal.*, Vol. XIII, p. 792.
MAGNUS, J. A. (1946).—*Brit. Jl. Ophthal.*, Vol. XXX, p. 692.
STEINBERG, T. (1943).—*Amer. Jl. Ophthal.*, Vol. XXVI, p. 846.

A CASE OF PSEUDO-GLAUCOMA

BY

J. A. MAGNUS

YORK

CASES showing typical glaucomatous cupping, but without increased intra-ocular pressure, have always aroused general interest. The various authors give them different names: amaurosis with excavation (v. Graefe), glaucoma without hypertension, primary cavernous optic atrophy (Schnabel), but I think Duke-Elder is right when he suggests that these terms should not be used. He calls these cases pseudo-glaucoma.

The following case is of interest because calcification of the internal carotid artery could be shown radiologically.

Robert Henry B., aged 74 years, was first seen on November 23, 1945. He had no complaints of anything in particular, he just *wanted new reading glasses.*

On examination the vision of the right eye was:—

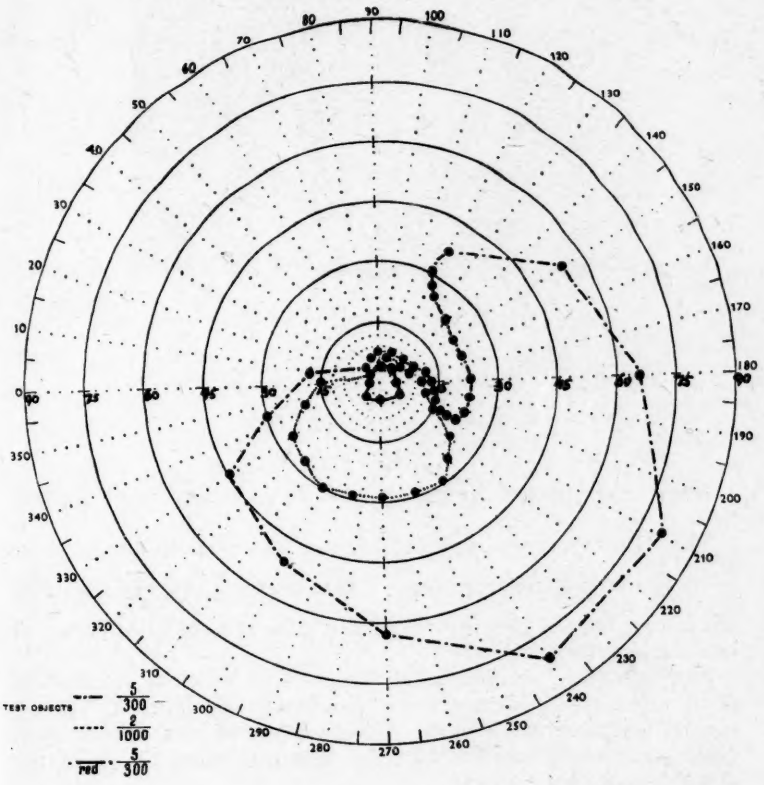
With $\frac{+0{\cdot}5}{-3{\cdot}5 \downarrow 90°}$ = 6/9 to 6/6 (2 letters)

that of the left eye:—

With $\frac{-1{\cdot}75}{-2{\cdot}75 \downarrow 90°}$ = 6/9 (3 letters)

With the addition of +2·50 reading small print (J.2).

RIGHT EYE



LEFT EYE

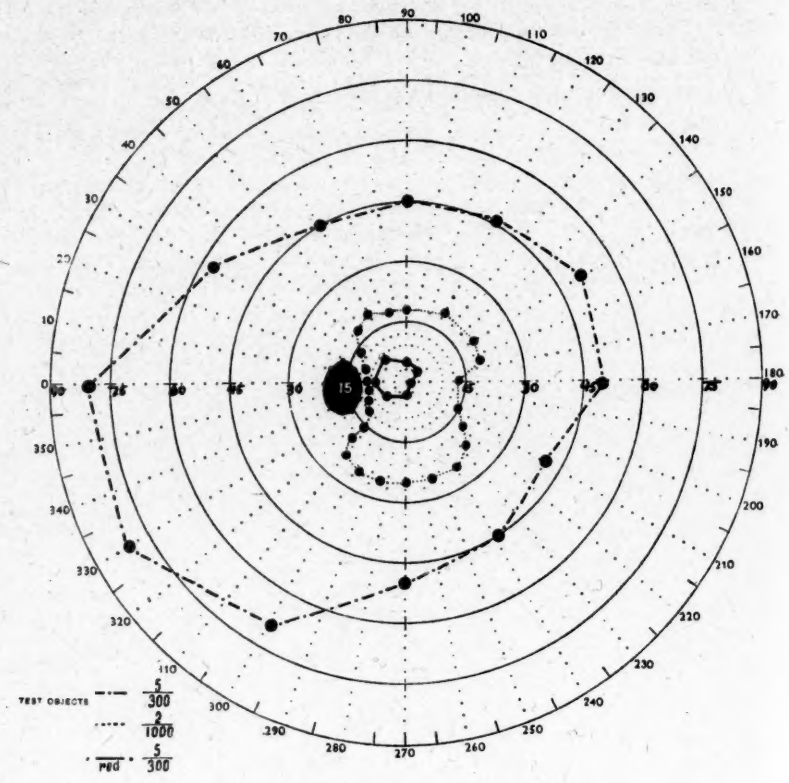


FIG. 1.

Both fundi showed deeply cupped discs, which were slightly pale.

The blood pressure was 160/80, and the intra-ocular pressure $\frac{5{\cdot}5}{6} = 19$ mm. Hg in both eyes. This pressure did not rise after one hour's stay in the dark-room, nor after repeated instillation of homatropine for one hour.

The right field showed marked nasal step, reaching the fixation point, and a typical arcuate nerve fibre bundle scotoma; the left one general peripheral depression. The field for red was, in both eyes, disproportionately smaller than the field for white. It is of the atrophic type (see Fig. 1).

FIG. 2.

See Schema on p. 695, Fig. 2.

The X-ray of the sella shows calcification of the internal carotid artery (see Fig. 2).

The question arises—is this case a glaucoma? The difficulty of the diagnosis lies in the fact that the fundi and the field defects appear to suggest this disease. The radiological finding is, therefore, of great importance, because it furnishes us with a reasonable explanation for the field defect, because the intra-ocular pressure was always found quite normal, even after provocative tests. The calcified internal carotid pressing on each temporal side of the chiasma has caused the nasal contraction, the nerve fibre bundle

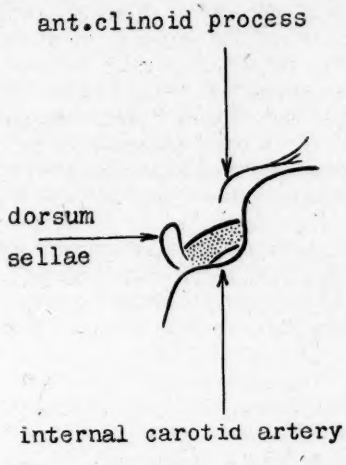


FIG. 2.

scotoma being most likely due to atrophic changes in the optic nerve itself.

Pickard pointed out that in glaucoma the fields for white and colours are similar, since all conduction is equally destroyed by pressure, but that in cases of glaucoma without hypertension, due to cavernous optic atrophy, the field for red shows a general contraction not in proportion to the contraction for white objects. The above case shows this disproportion of the fields.

It is difficult to find a reasonable explanation for the cupping of the discs, unless one assumes either a direct damage of the nerve fibres through pressure of calcified blood vessels, or areas of degeneration and softening within the optic nerve itself, through end-arteritis or spastic contraction of the nourishing blood vessels. If these areas of degenerated nerve fibre tissue are situated just behind the lamina cribrosa the latter will recede, and produce a glaucomatous cupping.

Redslob published in 1941 a number of cases of glaucoma without increased intra-ocular pressure, where the histological examination revealed typical cavernous atrophy of the optic nerve. These cases showed extensive vascular changes, due to venous stasis and Redslob thinks that the vascular upheaval is the responsible cause for the formation of the cavernous atrophy and the glaucomatous cupping.

Weekers, on the other hand, speaks of incomplete glaucoma. He says:—Glaucoma originates chiefly from a change in the intra-ocular blood vessel system. In the case of chronic glaucoma, *i.e.*, idiopathic glaucoma, the vascular alteration affects the uvea, the retina and the optic nerve, causing the three principal symptoms of glaucoma:—increased intra-ocular pressure, narrowing of the field of vision, and glaucomatous cupping of the disc. The three symptoms are usually, but not always, found simultaneously. There is an incomplete glaucoma: in certain cases the increased intra-ocular pressure may be absent. The incomplete glaucoma is observed in grown-up and aged patients, whose vascular system is more or less defective and the affection progresses very slowly, The cupping of the disc may remain isolated for a long time, but may, in course of time, be complicated by field defects. Occasionally hypertension may appear. These accompanying symptoms show that the lesion of the optic nerve must be attributed to glaucoma. There are a series of intermediate stages between monosymptomatic cupping without hypertension and complete glaucoma with ocular hypertension.

Taking all the various points into consideration I feel strongly that the above case does not fall into the category of monosymptomatic glaucoma, but that the calcified internal carotid artery proves a vascular cause. In favour of this are the atrophic type of the field changes, and the perfectly normal intra-ocular pressure, in spite of provocative tests. The field and fundus changes have remained stationary for over one year, a fact stressed by Thiel, who gives these cases a good prognosis.

Summary

A case of pseudo-glaucoma is presented, which shows field changes, deep cupping of the disc, normal intra-ocular pressure, and calcification of the internal carotid artery.

REFERENCES

NIELSON, ESTHER DALSGAARD.—*Acta Ophthal.*, 1937.
DUKE-ELDER, W. S.—Text-Book of Ophthalmology, Vol. III, 1940.
PICKARD, R.—*P.R.S. Med.*, Vol. XXIII, p. 57, 1930.
——— *Brit. Jl. of Ophthal.*, Vol. IX, p. 385, 1925
REDSLOB, E.—*Ann. d'Ocul.*, Vol. CLXXVII, pp. 323, 1941.
WEEKERS, R.—*Acta Ophthal.*, 1942.
——— *Acta Ophthal.*, 1943.
THIEL.—*B.O.G.*, Vol. XLVIII, p. 133, 1930, Heidelberg.

A CASE OF AN ADENOMA ARISING IN A SWEAT GLAND OF THE UPPER EYELID*

BY

F. CLIFTON *and* W. H. GORDON

LONDON

REPORTS of adenomata of the sweat glands are perhaps sufficiently rare to justify the description of a case where features are thought to indicate some points in the clinical diagnosis of these tumours.

Mrs. A.B., aged 70 years, seen recently as an Out-Patient, presented for examination a tumour of the left upper lid which had been increasing in size slowly over a period of five years. Clinical details of the early appearance of the lesion are not available, but it is known that the provisional diagnosis of ? sebaceous adenoma ? rodent ulcer, was made some time ago. The original lesion appears to have presented as a small crust on the skin of the lid near the inner canthus and adjacent to the margin.

On examination, there was present a rather flattened oval tumour with the long axis vertical, the lower pole of which overhung the lid margin, shielding also part of the caruncle from view. In size 1 cm. long and ¾ cm. broad, the smooth growth was covered by somewhat stretched though otherwise normal skin, movable over the tumour as a whole, but attached around the slightly raised edges of a small para-central crusted area. On palpation, the growth felt firm, yet not as hard as would have been expected in the case of an epithelioma. There was no regional glandular involvement and the tumour transilluminated freely.

Operation was performed by Mr. Eugene Wolff. A skin incision was made across the growth, which encapsulated in a thin fibrous sheath, was dissected out *en masse*, without difficulty. Small strips of redundant skin were removed from the margins of the incision which was closed by one silk suture. Healing was uneventful and rapid. The cosmetic result was very good, the lid appearing normal, save for the presence of a minute horizontal scar detectable on close examination.

Reference to the literature indicates that, in the past, extensive resections of the lid have been performed, with the necessity for subsequent plastic repair.

Pathology.—The skin is stretched over a tumour resembling in structure a tubulo-racemose gland. From the fibrous capsule, which is quite definite, except where the over-lying skin is

* Received for publication, June 4, 1947.

ulcerated, septa carrying well-formed vessels pass inwards to divide the tumour into lobules, and in turn give rise to finer strands supporting the branching tubules. In many places the fibres of this stroma are curiously swollen and ill-defined, occasionally so greatly that no structure can be made out, and the walls of many

FIG. 1.

Low power view showing the fibrous capsule and the numerous cysts.

of its blood vessels are similarly affected. The stroma is also infiltrated by lymphocytes which, here and there, form follicles.

Whilst in general the structure is tubular, in places there is proliferation of the parenchymal cells as solid masses, between some of whose cells cell-bridges can be made out. In these cell-masses are many degenerative cysts in all stages of development, from minute to quite large ones.

FIG. 2.

High power view of a cyst of type (1).

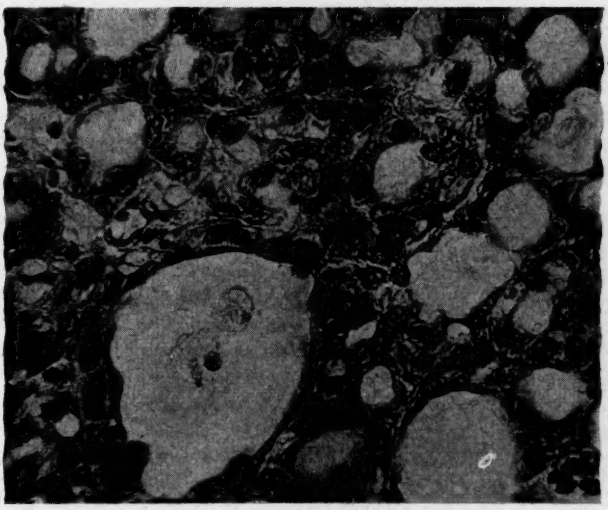


FIG. 3.

High power view of cysts (pseudocysts) of type (3). Degenerated tumour cells are seen within these.

A section of the tumour shows spaces or "cysts" of the following three types:—

(1) Lumina of tubules lined by columnar epithelium similar to that of the normal sweat gland, and having sometimes also an outer layer of cubical cells with oval nuclei which probably represent the myoepithelial cells of the normal gland.

(2) Lumina lined by smaller altered gland cells having denser nuclei.

(3) Cystic spaces due to breakdown of tissue cells, lined by partly degenerated polyhedral cells or in places merely walled by the stroma, and containing an albuminous coagulum and occasionally disintegrating parenchymal cells.

Summary

A case of adenoma of a sweat gland has been described and it is suggested that if consideration be given to the long history, the presence of the crust, the mobility of the skin over the edges of the tumour, the translucency, and the firm consistency, perhaps best tested with the blunt end of a probe for cystic spaces, a clinical diagnosis of this condition should be possible.

AN UNUSUAL CASE OF SYMMETRICAL, BILATERAL, NON-TRAUMATIC IRIS PROLAPSE.

BY

M. L. NAIRAC

MAURITIUS

A NEGRO woman aged 22 years, was transferred from the island of Rodriguez to the Civil Hospital, Port Louis, Mauritius, on March 29, 1947.

I here quote the report of the Government Medical Officer who first saw the case.

"Two weeks before she was seen, on March 15, she felt a strong, burning pain in the right eye followed by a discharge of 'pus.' The following day the left eye became similarly affected. The pain was such that the patient could not open her eyes and in her own words was blind for a few days."

"When first seen the patient was suffering from intense photophobia. Both eyes were found to have a staphyloma in the upper quadrant, the right side greater than the left. The pupils were irregular and drawn up. The walls of the herniation were so thin

* Received for publication, May 26, 1947.

that they threatened to rupture. They were transparent, however, and showed no signs of injury or inflammation."

"She was married 5 years ago and has three children; no miscarriages."

"She was transferred to Mauritius on March 27, 1947."

I saw the patient on April 1, 1947, and found the following condition:—

Both eyes had an iris prolapse between 11 o'clock and 1 o'clock, through gaps which measured 6 mm. by 4 mm. in the right eye and 6 mm. by 3 mm. in the left eye. The upper parts of the irides were well prolapsed through the openings and formed bulges: in

FIG. 1.

the right eye 6mm. × 4mm. × 3mm. and in the left eye 6mm. × 3mm. × 3mm. The pupils were drawn up towards the perforation more so in the right eye than in the left, but the edge of either pupil was not involved in the prolapse. The hole in each cornea was clear-cut, oval, and placed just central to the corneo-scleral junction. There were no signs of inflammation not even some ciliary injection near the prolapsed part of the iris. The rest of the cornea was bright and clear. The iris was normal in other respects; there were no posterior synechiae and its colour was normal. The anterior chamber below the prolapse was well-formed and the aqueous was clear. The fundi could be well-seen and were normal. There was no cupping of the discs.

Fig. 1 shows the condition, and although the photograph is not perfect it shows well the two bulges of the prolapsed irides, and the lack of inflammation. Kahn reaction was negative and there was no history of trauma. There was no evidence of avitaminosis. Atropine was instilled and the pupils dilated very well.

Treatment

It seemed obvious that it would be too great a gap to close with a conjunctival flap if the prolapsed part of the iris was abscised.

It was therefore resolved not to excise iris tissue but instead to cauterize it with the electric cautery along the whole of the prolapsed part and along the edge of the corneal hole, and then to apply a thick conjunctival flap which would thus adhere more readily.

On April 8, 1947, the left eye was done and the operation was carried out as planned.

On April 15, 1947, the flap having taken well, in the left eye, the other eye was similarly treated. But this time the iris was so thin that on the first impact of a not very hot cautery perforation occurred. We did not allow this to disturb the operation which was

FIG. 2.

carried out again as planned. The result was better than in the left eye.

Fig. 2 shows the condition after operation. This was taken on April 22, 1947.

On April 30, 1947, the patient was allowed out of hospital, and as far as one can tell has excellent sight and a strong conjunctival " patch " on either eye which should last her a long time.

The interesting problem here is one of aetiology. The probable explanation is of a bilateral acute infection, with the formation of corneal ulcers, which with the help of severe blepharospasm and probably a fair amount of rubbing perforated quickly and healed.

I do not think one can explain the condition in any other way. " Trophic " changes, avitaminosis, etc., would have shown other signs in the cornea and conjunctiva. These were lacking completely, nor was there any evidence of trauma. The curious thing is the symmetry of the lesions.

I would be glad to hear of any other similar case, or of any publication on the subject.

I am indebted to Dr. M. Shun-Shin, who first saw the case and brought it over Mauritius.

CONTRACTED SOCKET*†

The Splint Method of Post-operative Control

BY

F. MAXWELL LYONS

DIRECTOR, MEMORIAL OPHTHALMIC LABORATORY, GIZA, CAIRO

THE traditional Wheeler operation, an admirable concept upon which most later procedures have been based, was primarily intended for the *obliterated* socket in which no useful conjunctiva remained and where complete relining of the reconstructed cavity with an epidermal graft was necessary. In the majority of distorted and contracted sockets resulting from civil and war injuries, however, a considerable amount of healthy conjunctiva persists. Whether this should be conserved or removed as a preliminary to grafting has long been a subject of controversy.

The widespread prejudice against mixing skin and mucous membrane on the grounds that it produces chronic irritation and discharge I have found to be largely unsubstantiated or, at least, over-stressed. On the other hand, the sacrifice of all existing conjunctiva has very definite disadvantages. Total relining, at its best, produces a capacious socket but one which lacks resilience and adaptability. The normal shrinkage of the graft adherent to the tarsal plates inevitably results in thickening of the lids and entropion which may be pronounced and, even in lesser degrees, detract from the final cosmetic effect.

In very few contracted sockets is there insufficient conjunctiva remaining to cover the tarsal plates, and for many years I have been convinced that this should be carefully preserved.

The greatest source of trouble in any form of socket reconstruction is post-operative shrinkage. As in all Thiersch grafting, about 30 per cent. shrinkage of the epidermal inlay must be accepted as " normal " and duly allowed for in planning the graft. Unless the bed is properly prepared and freed from scar tissue, this shrinkage will be much greater and little or no benefit may result from the operation.

In spite of all precautions and in the most favourable cases, post-operative contraction is seldom regular and, although the resultant socket may be adequate in size, its irregular shape will prevent the fitting of a standard artificial eye. The ordinary stent

* The acrylic moulds and the method of splint fixation described in this communication were demonstrated at the Meeting of the Egyptian Ophthalmological Society held in Cairo in March, 1946.

† Received for publication, June 3, 1947.

or acrylic mould with pressure bandage will not satisfactorily control this shrinkage and distortion. All of us must have witnessed at times the disheartening sight of rotation, tilting and even extrusion of the mould two or three weeks after an apparently successful operation.

The technique of grafting and post-operative splintage here described was designed to offer controlled resistance to the forces of contraction and to persuade the socket, from the start, to take

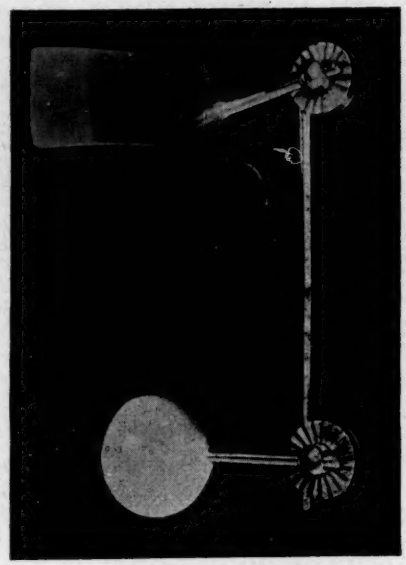


FIG. 1.

Showing arrangement of mould and the adjustable splint.

on and to keep the shape of a standardized prosthesis. It was arrived at by the gradual evolution of procedure and equipment in the course of a large series of cases undertaken during the war. In this I was greatly aided by the advice and practical help of colleagues—ophthalmologists, maxillo-facial surgeons, dental surgeons and mechanics.

Briefly, the epidermal graft is applied to the prepared socket in the usual way but on a special acrylic mould. At the first dressing (*i.e.*, on the 7th day) the mould is connected to a rigid but adjustable splint (Fig. 1).

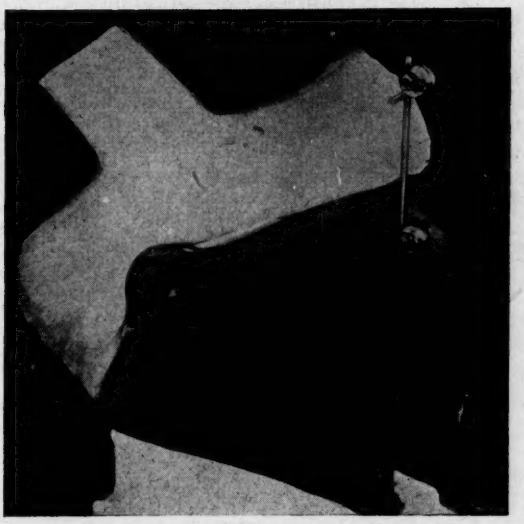


FIG. 2.

Plaster-of-paris head-cap and splint in position.

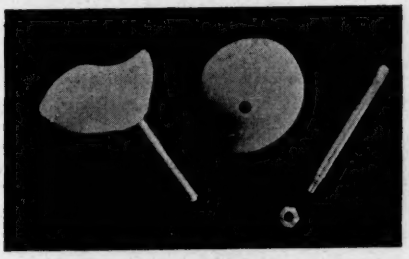


FIG. 3.

Showing details of mould and threaded rod. A nut similar to that shown in the photograph is embedded under the anterior surface of mould.

The fixed point is a frontal pin embedded in a plaster-of-paris head-cap and to this the mould is attached by stainless steel rods and universal clamps (Fig. 2).

The acrylic moulds are replicas of standard artificial eyes. Each mould has embedded below the anterior surface a small stainless steel nut (6 B.A.) into which a short length of rod, threaded at one end, can be screwed (Fig. 3). Latterly, Stallard's useful

suggestion—of drilling holes through the thickness of the mould to allow seepage of exudate and discharge from the back of the socket—has been adopted although it is not shown in the figures. A stock of 12 moulds, 6 right, 6 left, of sizes varying from medium to large covers almost all requirements.

Procedure

Anaesthesia.—General anaesthesia is preferable throughout the operation. Local anaesthesia is less satisfactory owing to the difficulty of blocking the nerves of the donor area of the upper arm. As a compromise, which has often proved useful, the dissection and preparation of the socket may be carried out under local anaesthesia and intra-venous pentothal given for the final stages of cutting and placing the graft.

Operation.—A wide canthotomy is first performed. The conjunctiva is then incised along a line corresponding with the *lower border* of the lower tarsal plate, extending from the outer canthus up to and behind the caruncle. Through this incision dissection is carried down to the infra-orbital margin, the periosteum of which is exposed throughout its length. This is an important step since the adhesions formed here help to anchor the lower fornix. Any redundant tissue is excised so that the tarsal plate covered with its conjunctiva may assume its normal vertical position. The caruncle should be preserved if possible.

The upper part of the conjunctiva is then freed from adhesions over the muscle stump and scleral remnants, if any. It is undermined and the upper fornix reformed, leaving the conjunctiva to cover the upper tarsus. Dissection here should be backwards rather than directly upwards and care must be taken to avoid injury to the levator muscle.

The conjunctiva should be delicately handled and any traction applied by holding-sutures rather than by forceps since pieces of graft may become adherent to the abraded surface and they are difficult to remove later. All fibrous bands must be carefully removed.

The largest mould over which the lids will close and which fits snugly into the lower fornix is selected by trial. It is removed from the socket, fitted with its short threaded steel rod and placed on one side ready to receive the graft.

Sutures for closing the canthotomy are inserted but left untied. All oozing is checked and the socket is lightly insufflated with penicillin and sulphathiazole powder. The area is covered while the graft is prepared.

A very thin epidermal graft, large enough to cover the mould and allow for overlapping, is cut. It is carefully eased off the knife into a bowl of warm saline so that it floats with its raw surface upwards. The mould, held by the attached rod, is insinuated underneath the graft and gently raised so as to lift the graft off the surface of the saline. With the aid of an iris repositor the graft can be evenly applied to the surface of the mould. If the graft is punctured over the posterior concavity of the mould it will readily subside into the slight hollow. Any redundant graft should be trimmed with scissors.

The socket is again examined to make sure that it is dry. Then, while an assistant retracts the lids, the graft and mould (still held by the rod) are lowered into the socket. The rod is unscrewed and removed, and the graft evenly spread over the anterior surface of the mould. The lids are closed and the canthotomy sutures are tied. It is not necessary to stitch the lids together although some prefer to do so. A tulle-gras and gamgee dressing is applied. Both eyes are covered with a firm crepe bandage.

The patient should be nursed flat or in a semi-recumbent position for the first two days; after that he may be allowed to sit up.

The dressings are left undisturbed until the 6th day. The bandages are then removed and the sound eye is uncovered. The dressing on the operated eye, if clean, is left *in situ* and fixed with adhesive strapping. A plaster-of-paris head-cap incorporating the metal frontal pin and plate is put on as shown in Fig. 2. First, a piece of stockinette is pulled over the head and over the ears. A single layer of crepe bandage is placed around the head and fixed with strapping; a similar piece of bandage is fixed across the top of the head in front of the ears. Next, a few layers of plaster-of-paris bandage are applied and reinforced over the frontal region. The pin and plate are now placed in position over the brow on the affected side and secured with several more layers of plaster bandage. For the sake of neatness, the stockinette is cut and folded back over the plaster and covered with a final layer or two of plaster bandage. It is left for 24 hours to harden. If the plaster is taken well down over the frontal region and under the occipital protuberance as shown in the figure, the head-cap will not lift off and will form a firm and steady support for the splint.

On the following day, *i.e.*, the 7th day after operation, the first dressing of the socket is done. The canthotomy sutures are removed. The lids are gently prised open and the rod is screwed into the hole in the mould. The mould is eased out of the socket. A pint of warm saline is poured over the socket and graft. Any pieces of redundant graft are removed. The excess saline is soaked up with a small piece of gauze. A few drops of penicillin (500

u/cc.) are instilled. The mould (with the rod attached) is dipped into sterile liquid paraffin and reinserted in the socket. It is then connected to the frontal pin by means of a suitable length of rod and two universal clamps. The position of the mould is carefully adjusted and the clamps are tightened with a spanner.

From that moment treatment becomes easy. The patient is allowed up and about. No dressing is required except a couple of thicknesses of gauze. The socket is irrigated daily without removing the mould. Twice a week the splint is taken down and the mould removed and cleaned. The socket is washed out and the mould and splint replaced. Slight adjustments of pressure, etc., may be required day by day.

There is no fixed time for keeping on the splint. Grafted sockets vary in their tendency to contract and in the period during which contraction is likely to continue. After three weeks a test may be made :—The clamps are removed and the rod unscrewed from the mould. If, after an hour or two, the lids show signs of gaping, the splint should be reapplied for another week. If, on the other hand, there is no attempt at extrusion, the splint may be left off until the following day, but a careful watch must be kept. The need for further splinting is decided by the course of events. It is usually necessary to retain the splint in position for three to five weeks after operation. The plaster head-cap is not removed until all risk of contraction is past. An artificial eye may then be fitted.

The operative procedure I have described is applicable to the partially contracted socket in which there is sufficient conjunctiva remaining to line the lids. The technique of post-operative splinting, however, is equally suitable for the totally obliterated socket in which all conjunctiva is lost, but a word of warning should be given here. In such a case, the remnants of the tarsal plates must be grafted and some degree of contraction and entropion will inevitably follow. If the fornices are rigidly fixed by the splinted mould, the contraction will necessarily have its effect near the lid margin and the entropion may thus be increased. This should be looked for and if signs of it appear the pressure of the splint should be relaxed a little or, if necessary, the mould should be changed for one of slightly smaller size.

The equipment required for the splint is easy to obtain. Stainless steel rod in 12 inch lengths and the universal clamps are supplied by Messrs. Down Bros. The " 6 B.A." nuts may be obtained from most ironmongers. The moulds incorporating the nuts can be copied in acrylic resin from selected artificial eyes by a dental laboratory. The threaded rod to fit the moulds and the frontal plate and pin can easily be turned out by any jobbing mechanic from a length of steel rod and a small strip of sheet brass.

The moulds and the rest of the splint can, of course, be used repeatedly.

Summary

1. The advisability of conserving healthy conjunctiva in a partially contracted socket is discussed.

2. Details of operation and a method of post-operative splinting of the mould are described.

REFERENCES

WHEELER, J. M.—*Amer. Jl. Ophthal.*, Vol. IV, p. 481, 1921.

STALLARD, H. B.—"Eye Surgery," p. 169, 1946.

ANNOTATION

The Milking-side Eye

The milking-side eye of a cow is the right side. One not infrequently finds that people refer to sides of the body in terms connected with their daily work. The Admiral who complained of pain in a tooth on the port side and Commodore Trunnion, whose larboard eye was missing, are examples from the seafaring point of view. All those who were born and bred in country districts must have visited the cow house to see milking in progress during their childhood days. That, and visits to the forge, were among the diversions of our own youth. One remembers that the milker sat on a three legged stool on the right hand side of the animal with the cheek alongside the flank of the cow and face directed towards the caudal end of the beast. If milkers sat in any other position the cow would be unable to see what was going on, might get restive and upset the pail. The importance of this in these austerity days can hardly be overestimated.

A correspondent recently wrote to tell us of a farmer who had asked him to have a look at one of his heifers which had something wrong with its milking-side eye, and we heard later that the owner had developed a conjunctivitis in his own right eye. It may be recalled that Angel Clare chose the milking time to declare his affection for Tess. "Old Pretty by this time had looked round, puzzled; and seing two people crouching under her where, by immemorial custom, there should have been only one, lifted her hind leg crossly."

In view of the mechanical aids practised in milking at the present

time we shall not be surprised, if in a few year's time, very few hand milkers will be left in this country. Handicraft is being superseded by mechanism; in our own opinion to the great loss of the amenities of village life. Few youngsters are taught nowadays to use a scythe and the same will soon be true of thatching. In the farm yard a Dutch barn solves this question and they were being used when we were a boy. But, with prefabricated houses, the old-fashioned thatched cottage will not last much longer.

The High Church parson who advertised in a local paper for "a communicant who can milk" could not have envisaged the time when it would be impossible to obtain the services of a milk-maid, whether a communicant or not. It seems worth while to rescue the milking-side eye from oblivion before it is too late.

CORRESPONDENCE

COLOUR VISION IN THE CONSULTING ROOM

To the Editors of THE BRITISH JOURNAL OF OPHTHALMOLOGY.

DEAR SIRS,—It is not easy to understand why Dr. Grieve still wishes to compare the percentage of colour defectives in my series of cases with the average found in the whole male sex. If the figures had been nearer to one another it would have pointed to a serious defect for, as I have stated, my cases were not chosen at random and some groups had been combed for defectives before coming to me. To criticise the low figure after my explanation is quite illogical.

I attempted to follow precisely the printed instructions when using the Ishihara plates, the Pseudo-Isochromatic plates, the Giles-Archer Colour Perception Unit, and the Edridge-Green Lantern, for details of which Dr. Grieve can peruse the relevant booklets. I have described the method of using my own lantern.

Dr. Grieve knows that for some years many of us were unable to avail ourselves of laboratory facilities, and investigations had to be carried out under adverse conditions. He must realise that it was quite impossible to have laboratory-calibrated scientific instruments built to special design, and improvisations had to be used. Now that these obstacles are removed the findings can be investigated in the laboratory, but 40,000 cases cannot be examined "when seated in an arm-chair by the fire"; conclusions drawn from small numbers of cases are inconclusive.

He is right when he states "the efficient testing of colour vision is no easy task." When I found some men who had been considered "normal," "safe," and "unsafe" by different specialists, I realised this, and conducted the investigation in an attempt to find improvements in the efficiency of the methods of testing, and in the apparatus used.

Yours sincerely,

FRANK R. NEUBERT.

HAUTERIVE,
THE QUEEN'S ROAD,
GUERNSEY.
October 10, 1947.

OBITUARY

G. W. THOMPSON

GEORGE WILLIAM THOMPSON died recently at the age of 82 years in Argentina. His medical education was obtained at Edinburgh University where he qualified in 1890. He became a Fellow of the Royal College of Surgeons of England in 1901.

When I knew him between 1900 and 1903 he was Chief Clinical Assistant to William Lang at Moorfields, and a very pleasant and unassuming fellow he was. He was Lang's Chief Clinical Assistant from 1898 to 1905.

His appointments included those of Surgeon to the Western Ophthalmic Hospital and Ophthalmic Surgeon to the French Hospital and to the Maida Vale Hospital for Nervous Diseases. He was a Member of the Ophthalmological Society, U.K., from 1905 to 1930.

He retired from practice some years ago. His address in the current number of the Medical Register is given as 11, Upper Wimpole Street. He paid me a friendly visit eight or nine years ago when I understood that he had interests in Argentina. I regret his loss.

A. F. MACCALLAN.

NOTES

Appointment

MR. PHILIP M. WOOD, M.B., Ch.B., D.O.MS., has been appointed Visiting Ophthalmic Surgeon to the Royal Halifax Infirmary.

* * * *

The Eye-Bank for Sight Restoration, Inc. New York City

NEW YORK CITY . . . . The Ophthalmic Society of New Zealand has recently organized an "eye-bank scheme for corneal graft material," according to word received at national headquarters of The Eye-Bank for Sight Restoration, Inc., 210 East 64th Street, New York City.

Dr. Cecil Pittar, an ophthalmologist in Auckland, New Zealand, in a letter asking for advice and assistance, describes the clearing house for corneas established by the Ophthalmic Society in his country. Dr. Pittar, who is acting as registrar for the new project, is notified by all hospitals and ophthalmic surgeons whenever it is planned to enucleate an eye with a good cornea. He is also notified by any surgeon who is in need of corneal graft material. Thus, he is able to arrange for the cornea to be transplanted within 24 hours.

It is planned to send enucleated eyes by air from one part of the country to another, Dr. Pittar writes. Plans are being made, also, to have "a pathological examination of the enucleated eye at the recipient end or to have the remains of the eye returned for pathological examination at the centre of the enucleation."

In response to Dr. Pittar's request, the New York Eye-Bank for Sight Restoration, Inc. has forwarded to him samples of the bottles and containers which are used for transporting eyes in the United States.

* * * *

The Ophthalmological Society of Australia

THE Ophthalmological Society of Australia proposes to hold its Eighth Annual General Meeting at Perth, Western Australia, on August 15-21, 1948, in conjunction with the Sixth Session of Congress of the British Medical Association in Australia.

The President of the Section of Ophthalmology of Congress is Dr. J. Bruce Hamilton, 174, Macquarie Street, Hobart, Tasmania, and the Honorary Secretary, Dr. John L. Day, St. George's Terrace, Perth, Western Australia.

Overseas visitors are cordially invited.